Typical and atypical functional specialisation within human prefrontal cortex

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Declaration

I, HSUAN-CHEN WU, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Abstract

The prefrontal cortex (PFC) plays an important role in a range of higher-level cognition including decision-making, social cognition, executing delayed intentions, and creative thinking. Previous studies have proposed a functional specialisation of the PFC region, and that this heterogeneity is associated with both structural and functional typicality between individuals. In order to examine this possibility, a reverse engineering approach was used to develop a PFC battery measuring behaviours relating to gambling, referential judgment, mentalizing, and faux pas detection. 107 typical-developing (TD) adults were recruited to establish the behavioural baseline, and identify the neural correlates of the measures in the PFC battery using voxel-based morphometry (VBM). The VBM analysis revealed significant relationships between different mental abilities and the size of different PFC sub-regions. Subsequently, 34 adults with autism spectrum disorder (ASD; a pathological group diagnosed with deficits on decision-making and social cognition) were tested on the new PFC battery. The results show that it provides new tools for detection of the ASD phenotype, and demonstrated the atypicality of ASD subjects when using single-case analysis. The thesis then turned to the functional specialisation of rostral PFC. A dissociation between lateral vs. medial rostral PFC activation was revealed when executing delayed intentions (the ability referred as prospective memory, or PM), compared with baseline ongoing activities. A novel PM paradigm for use with fMRI was designed to examine the specificity of PM cues. The results demonstrated the role that BA9/46 region plays in the detection of certain vs. uncertain future intentions. The final study examined cross-cultural differences in creativity, a cognitive ability thought to be substantially underpinned by frontal lobe structures. Matched adults from the UK and Taiwan were compared on adapted

version of standard measures of creativity. Cross-cultural differences were found on the novelty aspect of the creativity, but not on the usefulness aspect, which seemed to reflect different Eastern vs. Western self-construal. Altogether, the thesis used a range of approaches to highlight functional and structural variation within the PFC region and the mental abilities it supports, demonstrating some principles of organisation that exist across individuals, but also differences between individuals, and between populations of individuals.

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Publications

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Thiébaut, F. I., White, S. J., Walsh, A., Klargaard, S. K., Wu, H. C., Rees, G., & Burgess, P. W. (2015). Does Faux Pas Detection in Adult Autism Reflect Differences in Social Cognition or Decision-Making Abilities?. *Journal of Autism and Developmental Disorders*, 1-10.

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Chapter 1. Introduction of the thesis

In the developmental course of neuropsychology, the prefrontal cortex (PFC) was once considered almost ‘silent’ in terms of its role in human cognition, since large removals of the PFC region led to only mild disability (e.g., Mesulam, 1986), and there were no reliable measurement tool specifically designed to examine its functional role. However, the PFC remained ‘silent’ no more after an accident on a railroad construction site that changed the life of a foreman, Phineas Gage, forever, and the unofficial term ‘frontal lobe syndrome’ emerged out of Harlow’s report of this famous clinical case. Later on, consistent observations from other neurological case studies demonstrated that people could show remarkable deficits in a wide range of cognitions with ‘acquired’ lesions or damage to the PFC region. With the advance of neuroimaging techniques since the early 90’s, research into the PFC region has provided findings using various methodologies demonstrating converging evidence that the PFC region is involved in performance of all kinds of cognitive tests. This technology revolution in the field of cognitive neuroscience has established a new direction of investigating the function (human cognition) - structure (brain region) relationship in this fascinating cortical region.

One of the main issues with studying the functions supported by the PFC is its complexity in both functional and structural ways. Functionally, results from functional imaging studies provide only correlative rather than causative evidence, where the changes of hemodynamic signals indicate the particular region is involved with the underlying processes in a particular test, but are unable to identify whether the region is necessary for it. For example, a consistent finding of activations in brain region X is observed during performance of test measuring Y function, and it is easy to conclude that region X is essential for function Y. However, this link would be challenged if damage to region X led to mild change in performance of test measuring Y. Nevertheless, neuroimaging techniques do provide a more accurate localisation of the brain regions that associate with a given test. Furthermore, findings from functional imaging studies allow breaking down different cognitive abilities on a temporal scale, which could potentially compensate some difficulties when using neuropsychological method. For example, Bird, Castelli, Malik, Frith, & Husain (2004) reported a patient with extensive damages to the medial part of the prefrontal cortex, and this region was identified to be critical for ‘Theory of Mind’ using functional imaging technique. This mental ability is critical to make inference to other’s mind, but extensive experimentations failed to find any significant impairment using psychological tests measuring ‘Theory of mind’. This finding revealed the possibility that one patient alone could cause a complete rethink of a cognitive model, and this discrepancy between two different experimental methods highlighted the danger to use solely on imaging techniques to investigate cognitive neuroanatomy. Structurally, the PFC is one of the latest cortical structures to mature (Teffer and Semendeferi, 2012), and this unique characteristic enables this structure to adapt and connect to mostly every other regions in the brain (Alvarez and Emory, 2006). This indicates that investigation of the PFC region requires not only considering its relationship to other cortical regions (and/or the functions they support), but also requires considering highly variable individual differences that are secondary to heterogeneity of a person’s background experiences. As a result, it becomes increasingly likely that no cognitive function could be allocated to a specific cortical region in particular and exclusively, and one particular brain region supports only one cognitive function. According to the discrepancy on the function-structure relationship between different methods and the complexity of the PFC region, it seems necessary to combine different methodological approaches to have a better understanding of the underlying constructs supported by the PFC region.

Therefore, the aim of this thesis is to characterise the functions supported by the PFC region that either received little attention or have not yet been thoroughly examined. These include cognitive processes like decision-making to potential risks, making self-judgment, and interpersonal behaviours like understanding other’s mind, social embarrassment detection. Furthermore, the PFC also plays an important role in complex functions involve future performances like maintaining delayed intentions, and establishing new linkage or something new like creativity. In the current thesis, we implemented different methodologies and techniques from the field, and focused on capturing the variations of function-structure relationship in the PFC between individuals. Based on the cognitions that the PFC region supports, this thesis could be divided into three major sections, the first section discusses the cognitive processes on decision-making and social cognition aspects, the second section focuses on mental ability to anticipate future events, and the third section measures behaviours relating to creative thinking.

Chapter 2. Introduction of the PFC battery

2.1 The rationale of the PFC battery

In the field of cognitive neuroscience, one of the core issues was the mapping between anatomical structure in different brain region and the human behaviour it supported. The human PFC has been long proposed to play an essential role in higher-level human cognitive functions (Shallice, 1982). In human brain, different cytoarchitectural sub-divisions were shown to correspond well with clear functional boundaries in other cortical regions like primary motor and sensory cortices (see Kanai and Rees, 2011 for review). However, it reached little consensus on the mapping between specific cognitive functions onto anatomical sub-divisions in the PFC region (see Ramnani & Owen, 2004). The PFC was the largest single architectonic region of the frontal lobes (Christoff et al., 2001), and covered a significantly larger proportion of the cerebral cortex in human than in other species (Semendeferi, Armstrong, Schleicher, Zilles, & Van Hoesen, 2001). Furthermore, previous studies identified that the human PFC was involved with a range of complex cognitive processes, including multitasking (Burgess, Alderman, Volle, Benoit, & Gilbert, 2009), prospective memory (Burgess, Quayle, and Frith, 2001), self-judgment (Benoit, Gilbert, Volle, & Burgess, 2010), mentalizing (Gilbert, Williamson, Dumontheil, Simons, Frith, & Burgess, 2007), analogical reasoning (Volle, Gilbert, Benoit, & Burgess, 2010), and directing attending either to the external or internal states (Gilbert, Frith, & Burgess, 2005). Despite evidences from human neuropsychological studies, lesions, electrophysiological studies and neuroimaging studies demonstrated the ‘versatility’ of the PFC region, the way of this large brain region linked to various complex cognitive processes was not yet clear. For example, the ventrolateral part of the PFC (or inferior orbital frontal cortex), was associated with different but not mutually exclusive cognitive functions including task switching, reversal-learning, stimulus selection, and specification of retrieval cues (see Aron, Robbins, & Poldrack, 2014). It was fascinating that one sub-region of the PFC could account for a range of cognitive processes, and this unique nature intrigued us to use a reverse-engineering approach to examine the 'versatility' of the PFC region. In order to achieve this, we first focused on our region-of-interest, the PFC region, and then selected a range of behaviours that constantly shown to link with the PFC region. Next, we developed a set of new psychometric tests that putatively measured the cognitive functions behind these observable behaviours. We would then introduce the rationale and the basic settings of this set of new psychometric tests, the PFC battery.

In cognitive psychological studies, psychometric tests measuring different human behaviours were established, and experimentations were conducted to measure human cognitions ranged from basic cortical functions (e.g., visual, auditory, olfactory, somatosensory processing) to higher-level cognition (e.g., decision-making, social-cognition). With the advancement of neuroimaging techniques, massive and rapidly growing body of findings on human cognitive functions were identified. Nevertheless, studies focusing on measuring the same cognitive function using different techniques would face replication problem if researchers from different labs unable to find convergent results. To overcome this potential issue, Stuss et al. (2005) organised the Rotman-Baycrest Battery to Investigate Attention (ROBBIA) group of studies investigating performances of different sub-groups of prefrontal damaged patients on a set of neuropsychological tests between 1995 and 2005. The series of studies adopted several methodological approaches to control for potential artefacts in studying the functional-structural relationship of the PFC region using well-established neuropsychological measurements: 1) to use of different tasks with the same group of subjects; 2) to use the same subgroup to compare performances across all tasks; 3) to use of at least 10 subjects per subgroup; 4) to use of tasks involved with the same set of input and output processes; 5) to use of simple tasks so that the componential analysis would reveal reliable sets of processes. These principles were important guidelines when comparing the performances in different cognitive tasks measuring different subgroups of subjects, especially in lesion approach studies. In lesion-behaviour mapping literature, both single and group studies demonstrated theories of structure-function relationship in the PFC region (Shallice and Burgess, 1991; Burgess and Shallice, 1996; Stuss and Alexander, 2000). Compared with functional imaging studies, where hemodynamic changes in the same PFC region might be identified using very different cognitive paradigms, e.g., dorsolateral PFC: Duncan and Owen, 2000; rostral PFC: Burgess, Gilbert, & Dumontheil, 2007; Ramnani and Owen, 2004), lesion-behaviour mapping provided evidence that a brain region 'inactivated' and subsequently disrupted the linked function (D'Esposito and Postle, 2002). In lesion approach, findings showed that damage to a given PFC region impaired performance relating to a specific cognitive process by both association and dissociation of deficits using different tasks. Nevertheless, patients with frontal lobe damage in the PFC region are relatively rare to find, and it is beyond experimental control to restrict the lesions to small and specific sub-regions of the PFC area. On the other hand, in functional imaging studies, findings showed the same cognitive process activated the same PFC region by contrasting between conditions. However, this contrast method usually involved with unwanted cognitive processes during the task, and inevitably elicited signal changes that were not related to the functions to be measured. The inference of a functional role for the specific PFC region would be much stronger when converging evidence was established, and it seemed necessary to find another way to establish the function-structure linkage of the PFC region.

Amongst all kinds of neuroimaging techniques, functional magnetic resonance imaging (fMRI) provided measurement to the brain activity by detecting associated changes in regional blood flow, which was achieved by using the blood-oxygen-level dependent (BOLD) contrast to map neural activity in the brain when performing different experimental conditions. In order to integrate research findings and compare findings across different researchers, one of the ways is to use meta-analysis approach. Meta-analysis is a useful tool for quantitative analysis and for localising the brain regions that demonstrated consistent activations across different psychometric paradigms. Using this methodological approach, new theories could be developed based on the convergent location of the brain activations between different tasks, or even enabled researchers to identify groups of regions that consistently co-activated during the same task. However, meta-analysis approach has a potential issue relating to ‘specificity’ when considering the activations associated with different functions located in the same brain region (see Kober and Wager, 2010). For example, previous meta-analysis revealed that the ventromedial part of the prefrontal cortex (vmPFC) was activated when subjects performing tasks that related to reward processing. Nevertheless, it is obvious that observing activations in the vmPFC region do not necessarily indicate that the same cognitive function (e.g., reward processing) has occurred. To solve this issue regarding to specificity, two ways were proposed to justify the change of regional blood flow in the vmPFC region was *specific* to experiencing reward processing. First, to test the consistency of the activation observed in the vmPFC region by including all the tasks that involved reward processing. Second, to test the consistency of the NON-activation in the vmPFC region by reviewing all the tasks that does NOT involve reward processing. Both ways require intensive investigation and theoretically unable to achieve. Furthermore, the later way would possibly introduce false positive inferences that required proper statistical corrections, and eventually makes it even harder to justify the function-structure relationship in the vmPFC after proper corrections. The fundamental problem of the meta-analysis using fMRI data was that, the observed activations were established upon indirect mapping between the regional blood flow changes and the associated underlying processes intrigued by the designed psychometric paradigms. Moreover, the relatively poor temporal resolution and poor localisation of the activation in different PFC sub-regions also limited the interpretation of the findings. As a result, in order to examine the function-structure link more directly, we proposed to use a novel way of reverse-engineering method by using structural-based analyses instead of functional ones. First, we focus on one part of the brain, the PFC region, and developed a set of psychometric tests that measured functions relating to PFC evident by previous fMRI and neuropsychological studies. Next, we followed the principles suggested by the ROBBIA project (Stuss et al., 2005) to implement the same set of simple tasks on a large group of subjects, and eventually conducted componential analysis to examine the underlying sets of cognitive processes.

2.2 The establishment of the PFC battery

The establishment of the PFC battery could be divided into four stages. In the first stage, as mentioned above, we focused on the functions along two broad lines: decision-making and social cognition, which were evident to be supported by the

PFC region demonstrated by previous functional imaging studies. Using this reverse-engineering method, we designed four new psychometric tests adapted from previous studies measuring decision-making and social cognition, which presumably would involve neural activity in the PFC region evident by meta-analysis approach. In order to create a ‘functional’ baseline for the new PFC battery, a large group (N=107 subjects) of healthy typical-developing (TD) adults were recruited to administer the PFC battery. The aim of the first stage was to explore the behavioural data obtained from our newly-designed PFC battery, which allowed us to 1) compare our findings with previous relating studies measuring decision-making and social cognition, and 2) serve as the ‘functional’ baseline for further purposes.

In the second stage, we focused on investigating the ‘structural’ baseline of the PFC battery by establishing the function-structure relationship between the behaviours and the specific PFC sub-regions using a neuroimaging technique called voxel-based morphometry (VBM; Ashburner and Friston, 2000). T1-weighted structural scans were acquired from a sub-group (N=62 subjects) of the larger healthy typical-developing adults, who met the safety criterion and suitable for MRI scanning. This VBM technique enabled us to conduct regression analysis to localise the link between the behavioural performances of the PFC battery and localise the regional grey matter (GM) size of specific sub-regions in the PFC. VBM multiple regression analysis was conducted by using the behavioural performances extracted from the PFC battery in the first stage as covariate-of-interest. Furthermore, previous functional neuroimaging studies observed the association between different PFC sub-regions and different cognitive processes they supported in decision-making and social cognition. To test the established link demonstrated in relating functional imaging studies, we first identifed the region-of-interests (ROIs) in the PFC according to a human brain atlas called Automated Anatomical Labeling

(AAL; Tzourio-Mazoyer et al., 2002), and examined the function-structure relationships in a hypothesis-testing way. In order to achieve this, a lenient threshold ($p<0.001$, whole brain uncorrected) for exploration purpose was first applied to localise the GM clusters in the PFC region that correlated with the behavioural performance derived from the PFC battery. A further small volume correction (SVC) using the ROIs from the AAL atlas was applied to adjust for family-wise error (FWE) at $p<0.05$. The aim of the second stage was to investigate the functional-structural relationship between the behavioural performance measured by the PFC battery and different PFC sub-regions. This allowed us to: 1) identify the neural correlates of the PFC battery variables; 2) validate the behavioural performance measured by the PFC battery was associated with the GM volume in different PFC sub-regions; 3) examine the convergence between the location of the activation observed in relating fMRI studies and the structural-based VBM analysis.

The third stage of the PFC battery focused on comparing the baseline performance acquired from the typical-developing healthy adults with adults with Autism Spectrum Disorders (ASD). ASD individuals were diagnosed with impairments on social behaviours, repetitive mannerism, and deficits on language comprehensions (4th ed.; *DSM-IV*; American Psychiatric Association, 1994). Various kinds of psychometric experiments measuring behaviours associated with decision-making and social cognition demonstrated that individuals with ASD had difficulty processing interpersonal communications and manifested fixated behaviours with rigid interests. In imaging studies, both structural abnormalities in the PFC region and atypical functional specialisation were identified in individuals with ASD. These converging results on showing problems in decision-making and social cognition, along with functional and structural abnormalities in the PFC region, intrigued us to examine the atypical performance on ASD subjects. As a result, in the third stage, a group of adults diagnosed with high-functioning autism with IQ greater than 70 were recruited to administer the PFC battery. The aim of the third stage focused on examining the between-group difference on the ‘atypical’ responses in the ASD group, compared with the baseline performance of the typical-developing group established in the first stage.

The psychometric tests included in the PFC battery were described in each of the following four chapters, which included a gambling test measuring risky behaviours, a referential judgment test measuring response consistency, a video mentalizing test measuring the ability to make inference of other’s mind, and a cartoon faux pas test measuring detection of social norm violation. Each of the PFC battery chapter followed the three stages for establishing the PFC battery described above. First, set up the baseline performance for the PFC battery test by analysing the behavioural results of the 107 typical-developing (TD) healthy adults. In the second stage, to investigate the regional GM volumes in different PFC sub-regions that correlated with the derived variables from the PFC battery, we conduct VBM regression analysis by including 62 of the total 107 TD subjects, who were suitable for MRI scanning. In the third stage, we included the data acquired from the recruited 34 adults diagnosed with ASD and focused on the between-group difference compared with the baseline performance established by the 107 TD subjects using the experimental variables measured by the PFC battery.

2.3 Subjects recruited for the PFC battery

All the 107 subjects recruited for administering the PFC battery were aged from 18-70, native English speakers with no histories of hearing, visual or motor impairments. Subjects from both the TD and the ASD groups had estimated IQs derived from the National Adult Reading Test (NART; Nelson & Willison, 1991). For the VBM analysis, the TD sub-group with T1 weighted structural scans (n=62) and the TD group (n=107) were matched for age (t(167)=0.310, p=0.757), gender (χ^2=0.015, p=0.901), and NART derived intelligence scores (t(167)=0.982, p=0.327). For the TD vs. ASD comparisons, all ASD subjects had clinical diagnoses, and subjects from the TD group had no psychiatric or neurological disorders, or any ASD diagnosis amongst their first-degree relatives. Subjects in the ASD group (n=34) were diagnosed with high-functioning autism (2 subjects), Asperger's syndrome (25 subjects), or met the Autism Diagnosis Observation Schedule (ADOS; Lord et al., 2000) criteria for autism spectrum or autism from qualified clinician (7 subjects). In the ASD group, all the subjects had full-scale Wechsler Intelligence Quotients (FSIQ) greater than 80 (WAIS-III-UK, Wechsler, 1999; WASI, Wechsler, 1999), and 52 of the 107 TD subjects similarly had WAIS scores (all FSIQ greater than 80). The ASD and the TD subjects with WAIS scores (n=52) were matched for age (t(84)=0.558, p=0.578), gender (χ^2=0.862, p=0.353), Verbal IQ (t(84)=0.683, p=0.496), and Performance IQ (t(84)=-0.494, p=0.623). The other 55 TD subjects without WAIS scores were also included for analysis given no significant difference was found in NART derived intelligence (t(105)=-0.868, p=0.387) between the two TD sub-groups. Therefore, a total of 107 subjects in the TD group and 34 subjects in the ASD group were included for statistical analysis with comparable age (t(139)=1.607, p=0.110), gender (χ^2=1.907, p=0.167), and NART derived intelligence scores (t(139)=-1.413, p=0.160) see Table 2.1, for summary).

Table 2.1. The characteristics of the subjects recruited in the PFC battery.

	TD	TD with WAIS	TD sub-group [a]	ASD
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Subject number	107	52	62	34
male/female	58/49	30/22	33/29	23/11
Age	32.55 (10.62)	34.63 (10.20)	33.08 (10.78)	35.91 (10.63)
NART	115.77 (6.42)	115.21 (6.76)	116.77 (6.44)	113.85 (8.17)
Verbal IQ [b]		113.67 (12.59)		115.71 (14.78)
Performance IQ [b]		111.48 (12.75)		110.00 (14.79)
AQ [c]		15.86 (5.84)		35.50 (8.95)

[a] TD subjects with structural brain scans

[b] n=52 in the TD group

[c] n=37 in the TD group

2.4 Voxel-based morphometry

MRI data acquisition

T1 structural brain scans were acquired from a 3T Siemens MRI scanner at the Wellcome Trust Centre for Neuroimaging, London, UK. Three-dimensional Magnetisation Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence consisting of a 180 inversion pulse followed by a Fast Low Angle Shot (FLASH) collection (flip angle 12, TR=10 msec., TE=4 msec., TI=200 msec. and relaxation delay time 500 msec., field of view 250 x 250 mm) to give 128 contiguous slices of 1.88 mm thickness.

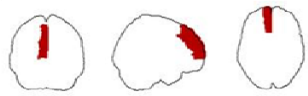
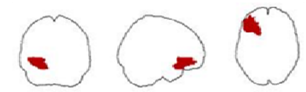
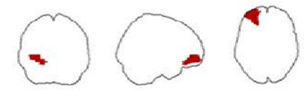
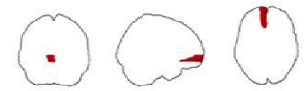
Voxel-based morphometry: pre-processing

All pre-processing procedures were conducted using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). Every subject’s T1-weighted structural images was first segmented into different tissue classes using unified segmentation procedure implemented in the “new segment” toolbox of SPM8 (Ashburner and Friston, 2005). The new segmentation procedure applied tissue probability maps including grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), soft tissue, skull, and non-brain regions to the T1-weighted structural image. This new segment toolbox used the prior probability maps to a given voxel belonging to a tissue class based on a previous finding using large sampled healthy adults across the lifespan (Good et al., 2001). The prior information is also combined with the distribution of voxel intensities using Gaussian mixture modelling and sampled every 3mm.

The GM tissue images created after segmentation were then used to generate a customised template using DARTEL method (Ashburner, 2007; Ashburner and Friston, 2009). Combining registration and spatial normalisation, DARTEL method used an iterative process to warp all the structural images into a common space and refine them progressively. For each participant’s image, flow fields were calculated during template generation which describe the transformation from each native image to the custom template. The information from the flow fields were then applied to each original image. To transform the images into the standard space, the custom template was registered to the tissue probability map using an affine transformation, which was incorporated during the warping process. When warping the structural images into a standard space, we used modulated normalisation to scale the intensity due to non-linear spatial normalisation by the determinant of the Jacobian transformation matrix at each voxel, which preserved the total amount of GM for each participant and provided a quantitative assessment of regional GM volume. Analysis performed on modulated images examined regional differences in the absolute volume of GM. The final step of the preprocessing involved in a smoothing procedure using an 8 mm FWHM by isotropic Gaussian kernel for statistical analysis.

Voxel-based morphometry: statistical analysis

The VBM multiple regression modelled the data with analysis of covariance (ANCOVA) including age, gender and total intracranial volume as covariates of no interest due to known effects based on a previous VBM study using a large sample of healthy adults (Good et al., 2001). A threshold masking using the absolute value of 0.1 was applied, which indicates the voxels included for analysis have at least 10% of grey matter. The variables from each of the task in the PFC battery were entered as covariates of interest in each ANCOVA model. For reporting the results, whole brain analysis included voxel values for each contrast constituted statistical parametric map of the t statistics were first set at a p value of $p=0.001$ for exploratory purposes. All the clusters in the PFC region above the lenient threshold were first reported. The clusters in the PFC region were further examined by multiple corrections at familywise error (FWE) $p<0.05$ using small volume correction (SVC; Worsley et al., 1996) implemented in the SPM software to test our a priori hypotheses. The binary images we applied for SVC were the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) derived from the Marsbar toolbox. The region-of-interest (ROI) for VBM analysis corresponded to different sub-areas in the PFC region, which included 1) the caudal part of the lateral orbitofrontal cortex: AAL_Frontal_Inferior_Orbital; 2) the rostral part of the lateral orbitofrontal cortex: AAL_ Frontal_Orbital_Middle 3) the medial part of the orbitofrontal cortex: AAL_ Frontal_Medial_Orbital; 4) the superior part of the medial prefrontal cortex: AAL_ Frontal_Superior_Medial. The projected illustration of each ROI region, the size of the ROIs, as well as the corresponding Brodmann area, were summarised in Figure 2.1. Further FWE corrections at $p<0.05$ for whole brain analysis was applied for exploring any voxels outside the PFC region. Resulting voxels were reported as x, y, z coordinates in MNI space, and were then converted to standard Talairach brain coordinates (Talairach and Tournoux, 1988) for labelling using Talairach Client. Clusters having more than 10 voxels (k>10) were reported

AAL ROI	Size (left/right)	Brodmann areas included	ROI projection
AAL_Frontal_Superior_Medial	23852 mm^3/16979 mm^3	BA8, BA9, BA10, BA6, BA32	
AAL_Frontal_Inferior_Orbital	13590 mm^3/13747 mm^3	BA47, BA45, BA11, BA46, BA13, BA10, BA25	
AAL_Frontal_Middle_Orbital	7112 mm^3/8057 mm^3	BA10, BA11, BA46, BA47	
AAL_Frontal_Medial_Orbital	5792 mm^3/6870 mm^3	BA10, BA32, BA24	

* The size, Brodmann areas included, and ROI projections are derived from the Online Brain Atlas Reconciliation Tool (OBART; Bohland et al., 2009).

Figure 2.1. The description and projection of the AAL ROIs used for VBM analysis.

VBM multiple regression analysis provided a tool to directly investigate the linkage between regional grey matter volumes and the experimental variables measuring cognitive behaviours. Hence, the VBM analysis here allowed us to 1) examine the functional-structural relationship established from previous related functional neuroimaging studies, and 2) test the theories based on previous meta-analysis using the hypotheses-testing approach. The behavioural and VBM results of each task in the PFC battery were described in the following sections.

2.5 The structure for the PFC battery chapters

In the following four chapters, we introduced each of the four psychometric tests included in the PFC battery, and organised each chapter in the same structure. In the first section, we described the behaviours we measure and their underlying functions. We reviewed previous relating studies examining the cognitions of our interest, and introduced the classic experimental paradigms measuring them. Next, we raised the potential issues or highlighted the inconsistent findings regarding to the functions supported by the PFC region, and proposed our hypotheses to the questions we would like to examine. In the second section, we described detailed methodology of each newly developed psychometric test, and the experimental measurements that designed for investigating the underlying processes of our interest. In the third section, we reported the behavioural results from the healthy TD subjects, and discussed the findings acquired from the TD subjects in the fourth section. In the fifth section, we reviewed previous imaging studies measuring the functions of our interest, and identified the specific PFC sub-regions that were evident to associate with those cognitions. In the sixth section, we showed the behavioural and the VBM results acquired from the 62 TD subjects with structural scans, and examined the function-structure relationship using a hypothesis-testing approach by conducting small volume correction to the ROIs that covered the PFC sub-region of our interest. The VBM findings of the TD sub-group were discussed in the seventh section. In the eighth section, we reviewed previous findings that observed impairments to the functions of our interest amongst ASD subjects, and proposed our hypotheses to the performance of the ASD group compared with the baseline performance acquired from the TD group. In the ninth section, we focused on the behavioural effects that showed significant between-group differences between the ASD and the TD group, and discussed the implications of the findings in the tenth section. After the four chapters describing the behavioural, VBM, and between-group effect of the PFC battery tests, we further took the PFC battery as a whole and investigated the between-test effect. In chapter 7, we conducted a range of statistical analyses including examining the effect of IQ and gender, principal component analysis, single-case approach analysis, logistic regression analysis for predicting group membership, and some preliminary ideas to the VBM findings across the four PFC battery tests.

Chapter 3. PFC battery – the gambling test

3.1 Measurements of risk-taking behaviour in response to potential wins vs. losses

In daily situations, people are often required to make decisions accompanied by uncertainty in various contexts. Using laboratory-based tests, psychological paradigms simulate open-ended scenarios, like making decisions under ambiguous situations, allowing individuals to implement their unique strategies, and adapt their decisions to changes of contexts accordingly. A commonly used psychological paradigm measuring decision-making involving uncertain outcomes is gambling. The key feature of gambling paradigms is the implementation of different experimental contexts, which provide opportunities to measure responses to potential rewards or punishments under different conditions. Another important feature is that the scores in gambling paradigms focus on measuring the likelihood of making risk-taking choices, or the pattern of responses between individuals, compared with variables measuring performance with absolute correctness like accuracy. A classic gambling test, the Iowa Gambling test (IGT; Bechara, Damasio, Damasio, & Anderson, 1994) offers subjects repeated deck selections associated with positive and negative outcomes, and subjects are required to make advantageous choices over time based on trial-by-trial feedback. It has been shown that healthy TD subjects are able to identify the advantageous deck and fixate upon it as the task progresses. Importantly, previous lesion and imaging studies has established the link between successful IGT performance and the PFC region (Bechara, Damasio, Tranel, & Anderson, 1998; Ernst et al., 2002; Northoff et al., 2006), which demonstrates the essential role of the PFC region played in risk-taking actions.

The IGT has provided well-established measures and consistent findings about adaptive learning of making advantageous choices during risky decision-making. Nevertheless, the IGT did not measure risk-taking actions to potential gains and losses separately, and people tended to implement different response strategies under different contexts. For example, the studies of prospect theory (Tversky and Kahneman, 1981) demonstrated that a sure choice was more appealing than a risky choice when it comes to potential gains, but it was the opposite when it comes to potential losses. This vulnerability to contextual changes indicated that people had different response patterns to uncertain rewards and losses. Another gambling paradigm, the Cups test (Levin, Weller, Pederson, & Harshman, 2007; Weller, Levin, Shiv, & Bechara, 2007), manipulated different levels of expected values (EVs), which described a concept taking both probability and monetary magnitude into account, and presented trials associated with potential gains and losses in separate blocks. This manipulation provided an opportunity to measure risk-taking behaviours when facing potential rewards and punishments separately. In the Cups test, some options provided sure outcomes, and some options were risky ones. The risky options were accompanied with a range of EVs varying at nine levels, and subsequently made some combinations of sure vs. risky choices 'risk advantageous' (RA), some 'risk disadvantageous' (RD), and some had 'equal expected values' (EQEV). Previous studies using the Cups test revealed that healthy TD subjects made more risk-taking behaviours with increasing EVs of the risky options on gain trials, and fewer risk-taking behaviours with increasing EVs of the risky options on loss trials. It was interpreted that be able to adjust the propensity to make risky decisions demonstrated sensitivity to the manipulations of EVs. In addition, a higher risk rate to potential losses than to gains was found in healthy adults (Levin et al., 2007), and this domain-specific strategy to potential rewards vs. punishments was consistent with the classic cognitive bias of the framing effect (Tversky and Kahneman, 1981). Evidence from neuropsychological studies further established the link between performances in the Cups test and the PFC region. In Weller et al. (2007), patients with lesions to the ventromedial part of the PFC region displayed insensitivity to manipulation of EVs by showing more risk-taking behaviours to RD trials in the loss domain than control subjects did. Xue, Lu, Levin, Weller, Li, and Bechara (2009) used fMRI on the Cups test and defined the risk rate on EQEV trials as an index of 'risk preference', where the risky and the sure options had identical EVs without favouring either decision. The imaging results found that neural activation in the ventromedial PFC was positively correlated with individual's risk preference in the win vs. loss contrast. These converging results demonstrated that the Cups test provided useful measurements to investigate risk-taking actions to potential gains and losses separately, and showed a function-structure relationship between risk preference and a specific PFC sub-region.

Following the rationale of the Cups test, we developed the gambling test of the PFC battery to measure risk-taking behaviours under various contexts to our recruited subjects. The first part of the modification focused on the experimental stimuli. The original Cups test used the number of 'cups' to illustrate three levels of probability and 3 levels of monetary magnitude to form a total 9 levels of EVs. In the current gambling test, we used pie charts to depict four levels of probability, and the number of £1 coin photos to depict four levels of monetary magnitude to form a total 16 levels of EVs. The second modification was the experimental design of the trials. As in the original Cups test, each trial consisted of a risky option varying in EVs and a sure option with certain outcomes, where different combination of risky vs. sure options yielded experimental conditions that were labelled as RA, RD and EQEV trials. Critically, the same combinations were presented multiple times in the current gambling test, and this multiple exposure manipulation enabled us to measure the ‘consistency’ of responding to particular options, which was then referred as the ‘repetitiveness’ variable in later sections. To elaborate on this repetitiveness variable, each combination (e.g., a 50% chance to win £2 vs. a 100% chance to win £1) was presented nine times in the win and the loss conditions respectively. By definition, repetitive behaviours involved with making the same decision multiple times under different contexts, and the mental process relating to making adjustments in accordance with task demands, or cognitive flexibility, was evident to associate with the PFC region (Rougier, Noelle, Braver, Cohen, & O’Reilly, 2005; Kim, Johnson, Cilles, & Gold, 2011). A robust phenomenon observed in gambling paradigms revealed that individuals tended to fixate on risky options when receiving rewards as a positive reinforcement, and tended to show a shift of risk-taking behaviours when receiving punishment as a signal to change, or the ‘win-stay, lose-shift’ principle. To examine this cognitive bias relating to repetitive behaviours in gambling, we further calculated the repetitiveness, a variable highlighted the option-based response pattern to different gambling contexts besides examining the likelihood to make risky actions (i.e., risk rate) to EQEV, RA and RD trials,. More details of this repetitiveness variable were given in the Methods section. Lastly, we used block design and always showed the win block first, then the loss block. Compared with gambling paradigms that interleaved win and loss trials (e.g., De Martino, Harrison, Knafo, Bird, & Dolan, 2008), it is possible that constant shifts between domains might cause subjects unable to establish a mental set specifically for a particular context. Therefore, the current gambling test used a block design that enabled subjects to develop a strategy or engage in a rewarding or punishing mode in a period of time.

Furthermore, the win condition always came first, and then the loss condition, which allowed us to establish a stable baseline between individuals when examining any effect relating to switch of domains, e.g., a between-subject balance of the block order (win then loss vs. loss then win) would introduce two potentially distinct sets of strategies given that people tended to process potential wins and losses differently. The aim of this section was to establish the baseline performance of the gambling test, which included measuring risk rate, repetitiveness, and reaction time in the win and loss conditions separately. Based on previous findings using the Cups test, we hypothesised that TD subjects would show sensitivity to varying levels of EVs in the win and the lose conditions. Furthermore, we hypothesised that TD subjects would demonstrate the classic framing effect by making more risk-taking actions when facing potential losses than to wins. Lastly, based on the 'win-stay, lose shift' principle in gambling, we expected to observe a higher level of consistency, or the repetitiveness in the current paradigm, to wins than to losses.

3.2 Methods of the gambling test

Materials and Design

The gambling test consisted of a win condition and a loss condition, and each condition contained 144 trials. In each trial, subjects were asked to choose between a risky option and a safe option presented side-by-side on the screen. All the options were illustrated by pie charts demonstrating varying levels of probability to win/lose a certain amount of imaginary money, and pictures of £1 coins demonstrating varying levels of monetary magnitude. The sure options were always illustrated by a pie chart showing a 100% chance to win/lose a £1 coin (i.e. no "chance" at all). The risky options, on the other hand, were illustrated by pie charts varying in 4 levels of probability (20%, 25%, 33%, or 50%) to win/lose 4 levels of money (£2, £3, £4, or £5) (see Figure 3.1). Compared with the original Cups test having 9 levles of EVs, the current gambling test had 16 levels of EVs ranging from £0.4 (20% x £2) to £2.50 (50% x £5) depicted by the risky options. Subsequently, the combinations of EVs could be divided into three categories: 1) risk advantageous (RA) trials: combinations that favoured risk-taking behaviours with higher EVs in the win condition and lower EVs in the loss condition; 2) risk disadvantageous (RD) trials: combinations that favoured risk-aversive behaviours with lower EVs in the win condition and higher EVs in the loss condition; 3) equal expected values (EQEV) trials: combinations that favoured neither risk-taking nor risk-aversive behaviours with identical EVs to the sure options in the win and the loss conditions.

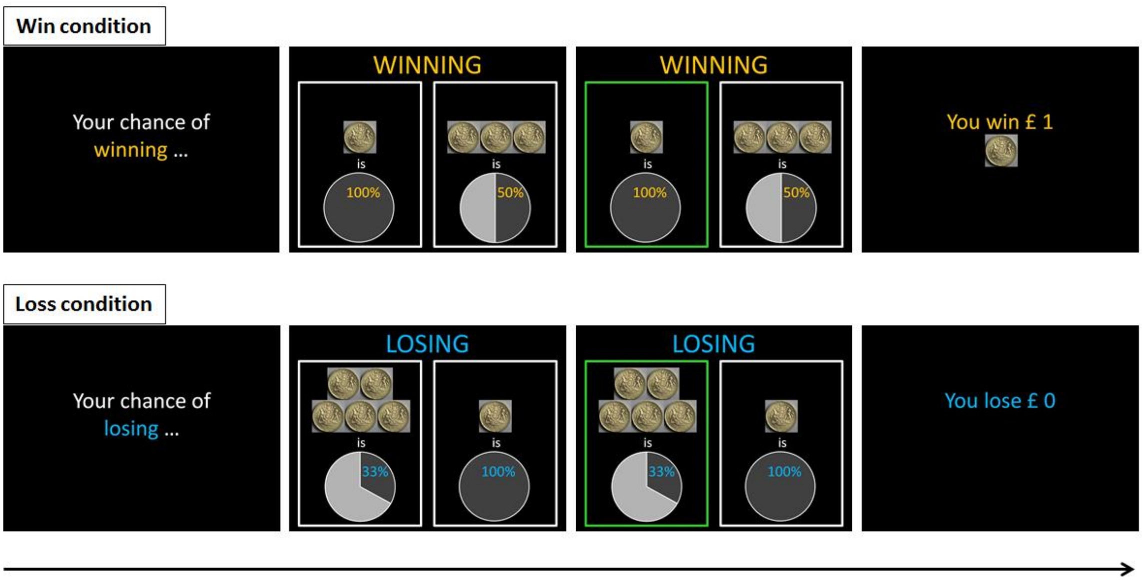


Figure 3.1. The experimental procedure of the gambling test. All subjects administered the win condition first, then the loss condition. In this illustration,

subjects were required to choose from a sure option to win £1 vs. a risky option to have 50% chances to win £3 in a winning scenario. In the depicted losing scenario, subjects were required to choose from a sure option to lose £1 vs. a risky option to have 33% chances to loss £5.

The win and the loss condition each comprised of nine blocks, and there were 16 trials in each block. In each block, 16 kinds of combinations (safe vs. risky options) varying in EVs appeared once. A proportion of positive outcomes (25%, 50%, or 75% of the trials) were pre-determined in each block. The order of all trials was presented in an identical order across all subjects, which was to ensure that all subjects received the same testing experience during the gambling test. The position of the sure and risky options presented on the screen was counterbalanced.

Procedure

The gambling test was presented on a laptop using MATLAB R2008a (The MathWorks) and stimuli were presented by the Cogent toolbox v1.32 (http://www.vislab.ucl.ac.uk/Cogent). Subjects were told that they would be given several chances to win and lose some imaginary money, and were encouraged to end up with as much money as they can. All subjects performed the win condition first, and then the loss condition.

During each trial, a cue saying 'Your chance of winning/losing…' would be presented on the screen for 500 milliseconds in the win and the loss condition, and a trial depicting a sure option and a risky option were presented side-by-side on the screen. Subjects were told to choose either the sure or the risky option by pressing one of the corresponding keys (the left or the right arrow key). Each trial stayed on the screen until a decision was made. After responding, the option selected was highlighted with a green border for 300 milliseconds, and the outcome of that trial was presented on the screen for 700 milliseconds. If participants chose the sure option, the outcome would always be ‘You win £1’ in the win condition and ‘You lose £1’ in the loss condition. If subjects chose the risky option, the outcome would be ‘You win £0/£2/£3/£4/£5’ in the win condition, and ‘You lose £0/£2/£3/£4/£5’ in the loss condition depending on the pre-determined probability for positive outcomes in the given blocks. There were two 10 second breaks at the end of the third and the sixth blocks in the win and the loss conditions. The gambling test took each subject approximately 20 minutes to administer.

Measurements

We focused on the analysis of three variables in the gambling test: (1) risk rate, the likelihood to make risky decisions; (2) overall reaction times, the latent period to make responses; (3) repetitiveness, the consistency of making the same decision to each combination that varies in EVs. Unlike risk rate that measured the overall risky performance across all combinations, the repetitiveness variable measured response pattern to each particular combination. To elaborate on this, what we tried to measure was the consistency of making choices when presented same combination several times. For example, a trial depicting ‘a 50% chance to win £2 vs. a 100% chance to win £1’ appeared 9 times in the win condition, so the frequency to take a risk to this combination was ranged from 0 to 9. A newly-assigned score out of a maximum possible 9 instances is followed by: 0->5, 1->4, 2->3, 3->2, 4->1, 5->1, 6->2, 7->3, 8->4, and 9->5. This ‘V-shape’ weighting scheme gave higher scores to both extreme risk-taking and risk-avoiding behaviours. On this basis, to take a risk on one particular combination 4 or 5 out of 9 times can be considered ‘less repetitive’, and as subject chose to take a risk on that particular combination 0 or 9 out of 9 times can be considered ‘highly repetitive’. Following this logic, we first calculated the frequencies for each subject to take risks on combinations varying in 16 levels of EVs, and then transformed the frequencies according to the ‘V-shape’ transformaiton to yield a repetitiveness score. We summed the repetitiveness score and scaled this score according to a range of possible maximum and minimum values into percentile for statistical analysis. For example, amongst the total 144 trials, if a subject chose the ‘50% chance to win £2’ over the ‘a 100% chance to win £1’ option every time this combination appeared (9 times in total), and never chose the risky option to the rest of the 135 trials. Risk rate would give a 6.25% (9/144), but repetitiveness would show 100, a perfect repetitive behaviour.

In order to examine risky behaviours on trials varying in EVs under different conditions, repeated measures ANOVAs with condition (win and loss) and EVs (RA, EQEV and RD) as within-subject factors were conducted to examine the main effects and interactions on risk rate and repetitiveness. However, due to extreme risk-taking or risk-avoiding behaviours, reaction times under some EV combinations were not available, e.g., a conservative subject would have no, or very little reaction time score for RD trials. Hence, the reaction times were collapsed across EVs and analysis was conducted using paired t tests to compare the effect between domains (win vs. loss).

3.3 Behavioural result of the TD group

Experimental variables including risk rate, repetitiveness, and reaction time were entered into repeated measures ANOVA with condition (win vs. loss) and EVs (RA, EQEV, RD) as within-subject factors. The behavioural result of the gambling test in the TD group were summarised in Table 3.1.

Table 3.1. The mean and standard deviations of risk rate, repetitiveness, and reaction time (msec.) overall, and to RA, EQEV, RD trials in the win and the loss conditions were summarised separately.

Condition	Variable	EV	mean	SD
Win				
	Risk rate			
		Overall	0.42	0.20
		RA	0.71	0.26
		EQEV	0.39	0.28
		RD	0.15	0.20
	Repetitiveness			
		Overall	0.69	0.18
		RA	0.78	0.24
		EQEV	0.62	0.24
		RD	0.73	0.20
	Reaction time (msec.)			
		Overall	1384.4	494.4
Loss				
	Risk rate			
		Overall	0.52	0.21
		RA	0.72	0.24
		EQEV	0.49	0.26
		RD	0.33	0.28
	Repetitiveness			
		Overall	0.59	0.22
		RA	0.66	0.24
		EQEV	0.58	0.25
		RD	0.63	0.24
	Reaction time (msec.)			
		Overall	1472.8	646.8

Risk rate

To test the sphericity of the EV variable, Mauchly's test first revealed that the assumption of sphericity had been violated (χ^2 (2)=70.739, p<0.00), and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε=0.671). However, the condition x EV interaction has met the assumption of sphericity (χ^2 (2)=1.302, p=0.521), so there was no correction of the F-ratios for the interaction effect. Repeated measures ANOVA of risk rate revealed a significant main effect of condition (F(1,212)=12.946, p<0.001, where TD subjects took significantly more risk-taking actions in the loss condition than in the win condition. Repeated measures ANOVA also identified a significant main effect of EVs (F(1.342, 209.418)=271.132, p<0.001), and post-hoc test using Bonferroni correction confirmed that TD subjects made more risky decisions in the RA>EQEV>RD order (all pairwise comparison p<0.001). Importantly, repeated measures ANOVA found a significant condition x EV interaction (F(2,212)=31.098, p<0.001). Follow-up analysis showed that the interaction was driven by more risk-taking behaviours to EQEV and RD trials in the loss condition than in the win condition, but risk rate to RA trials was comparable between the win and the loss condition.

Repetitiveness

Mauchly's test of the EV variable first found that the assumption of sphericity was met (χ^2 (2)=1.795, p=0.408), as well as the condition x EV interaction (χ^2 (2)=4.904, p=0.086). As a result, we did not correct for the degrees of freedom of the F-ratios. Repeated measures ANOVA on repetitiveness revealed a significant main effect of condition (F(1,212)=19.635, p<0.001, where TD subjects demonstrated significantly higher repetitiveness in the win condition than in the loss condition. Repeated measures ANOVA also revealed a significant main effect of EVs (F(2,212)=26.780, p<0.001), and post-hoc test using Bonferroni correction identified that the level of repetitiveness on risk-taking behaviours was in the RA>RD>EQEV order (all pairwise comparisons p<0.05, except for RA vs. RD p=0.053). Furthermore, repeated measures ANOVA found a significant condition x EV interaction

(F(2,212)=3.047, p=0.05). Follow-up analysis showed that the interaction was contributed by a much higher repetitiveness to RA and RD trials in the win condition than in the loss condition, but the repetitive behaviour was comparable to EQEV trials between conditions.

Reaction time

Paired t test showed that the difference between the win and the loss conditions was not significant (t(106)=-1.836, p=0.069).

Correlation analysis

In order to investigate the relationships between the three variables, we collapsed risk rate and repetitiveness across varying levels of EVs to enable correlation analysis with reaction time. Spearman's rank-order correlation analysis was conducted in two different approaches. In the first approach, we focused on the within-variable effect, where the relationships on risk rate, repetitiveness, reaction time between the win and the loss conditions were examined. In the second approach, analyses on the between-variable effect were conducted, where the relationships between the win and the loss conditions using risk rate, repetitiveness, and reaction time were examined separately.

In the first approach, correlation analysis revealed that the relationship between risk rate in the win and the loss condition was not significant (r_s (107)=0.100, p=0.307). A positive significant correlation was found between repetitiveness in the win and the loss conditions (r_s (107)=0.441, p<0.001). Analysis of reaction time revealed a positive significant correlation between the win and the loss conditions (r_s (107)=0.752, $p<0.001$). In the second approach, correlation analysis between variables revealed a negative significant relationship between risk rate and repetitiveness in the win condition (r_s (107)=-0.457, $p<0.001$). No significant correlations were found in the win condition between risk rate and reaction time (r_s (107)=-0.112, $p=0.252$), neither as between repetitiveness and reaction time (r_s (107)=0.105, $p=0.280$). On the other hand, between-variable correlation analysis in the loss condition identified a negative significant relationship between risk rate and reaction time (r_s (107)=-0.252, $p=0.009$). No significant correlations were found in the loss condition between risk rate and repetitiveness (r_s (107)=0.011, $p=0.912$), neither as between repetitiveness and reaction time (r_s (107)=0.077, $p=0.431$).

3.4 Discussion of the behavioural result in the TD group

The gambling test examined individuals' risk-taking behaviours under varying levels of EVs between the win and the loss domains separately. First, repeated measures ANOVA of risk rate demonstrated that healthy TD subjects had sensitivity to the manipulations of EVs by taking more risks to trials in the RA>EQEV>RD order. This indicated that TD subjects made their risk-taking behaviours in a rational way by adjusting their propensity to potential uncertainty in accordance to EVs. The significant main effect of condition displayed more risk-taking behaviours to potential losses than to gains, and this domain-sensitive bias was consistent with framing effect (Tversky & Kahneman, 1981). Furthermore, a significant interaction between condition and EV on risk rate was identified, which demonstrated an increasing loss averse strategy to EQEV and RD trials, but comparable to RA trials between domains. This suggested that the cognitive bias (e.g., framing effect) was only observed under fair or disadvantageous situations, yet under situations that strongly favoured risk-taking actions, TD subjects did not show a higher loss-aversive strategy than to potential gains. It was proposed that an irrational emotional interference over rational cognitive process that contributed to framing effect (see De Martino et al., 2008). In the current paradigm, it was possible that TD subjects experienced comparable emotional interference to RA trials in both win and loss domains, where the chance of gaining extra reward and the change of avoiding extra punishment was greatly favoured, and subsequently led to a comparable propensity to take a risk rather than played it safe.

Besides risk rate, we further calculated the repetitiveness variable that measured the response pattern to different combinations. Repeated measures ANOVA of repetitiveness revealed a significant main effect of EV, which indicated that the rigidness of responding was in a RA>RD>EQEV order. This finding indicated that the decision to each appearance of the same combination was more random, and subjects were the least decisive to EQEV trials. The repetitiveness was the highest to RA trials, which showed that the response pattern was the most fixated under situation favoured risk-taking behaviours. This also supported that TD subjects were sensitive to the manipulation of EV, where subjects made more risky decision, and made them consistently. Analysis of repetitiveness also found a significant main effect of condition, which showed that subjects responded more repetitively in the win condition than in the loss condition. This was in accordance with the 'win-stay, lose-shift' principle in gambling paradigms, and suggested that the response pattern was more susceptible in the loss condition than in the win condition. Interestingly, repeated measures ANOVA identified a condition x EV interaction showing higher repetitiveness to RA and RD trials to wins than to losses, but in a comparable way to EQEV trials between domains. This result was similar to the selective framing effect observed on risk rate, which showed that the 'win-stay, lose-shift' principle applied only to situations that favoured either risk-taking or risk-avoiding actions. When it comes to situations that favoured neither option, the response pattern was comparable beween domains due to higher degree of randomness. Analysis of reaction time found no significant difference between the win and the loss condition, which indicated that TD subjects spent comparable time making decisions to potential wins and losses, and further suggested that the risky decision-making processes to potential rewards or punishments was equally demanding amongst TD subjects.

In order to examine the relationships within and between variables in different conditions, correlation analyses were conducted in two approaches. In the first approach, analysis of within-variable effect found that the correlation between risk rate in the win and the loss conditions was not significant. This suggests that the propensity to take risks when evaluating potential gains and losses involved with distinct cognitive processes, where taking fewer risks to gain more rewards does not necessary associate with fewer loss-aversive actions to avoid more punishments. On the other hand, correlation analysis of repetitiveness and reaction time demonstrated positive significant relationships between domains. These significant relationships suggested that the repetitive pattern, as well as the response speed to risky decision-making was less domain-specific, where a general guideline was implemented for processing potential wins and losses in each individual. In the second approach, the relationships between variables were examined in the win and the lose condition separately. In the win condition, a negative significant correlation between risk rate and repetitiveness was observed, whereas no significant correlation was found between risk rate and repetitiveness in the lose condition. This indicated that, for example, the fewer risk-taking actions accompanied with higher repetitive response patterns in the win condition, but this is not necessarily true in the lose condition. Analysis of the skewness of the overall repetitiveness in the win condition showed a value of -0.5, which indicated that the tail on the left side was longer than the right side, compared with a value of -0.355 for the overall repetitiveness in the loss condition. The difference of skewness suggested that the lower risk rate to wins than to losses reflects a more confined risk-taking preference to potential wins, where risky decisions were made to particular options (demonstrated by risk rate) and subjects further fixated on them (indicated by repetitiveness). In the lose condition, one the other hand, TD subjects were more willing to take risks in order to avoid potential losses. This might subsequently lead to a higher propensity to make risk-taking actions as a whole (demonstrated by risk rate), and a less confined resonse pattern on risk-taking preference (indicated by repetitiveness). This domain-specific strategy was consistent with the classic 'exploration – exploitation' dilemma, which delineated the mind of gamblers trying to optimise decisions on the basis of accumulated experience, the richest option, and the learning process from choosing less familiar option with bigger potential. Previous studies have identified the PFC region played in supporting this trade-off mechanism between executing and not executing a given action (Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006; Cohen, McClure, & Yu, 2007). Lastly, the null relationships between the overall reaction time and other two variables indicated that longer consideration did not accompany systematic increase or decrease in the propensity to take risks, and the repetitive response pattern.

3.5 Neuroimaging findings of risk-taking behaviour to potential wins vs. losses

The gambling paradigm used here provides laboratory-based measurements of risk-taking behaviours when facing uncertain situations accompanied with potential rewards or punishments. Previous theoretical accounts have argued that the decisional process could be based on rational consideration (e.g., sensitivity to manipulation of varying EVs) with different strategies (e.g., exploration vs. exploitation) under different contexts (e.g., the framing effect). As discussed earlier, one of the critical features of the gambling paradigm was that the scores allowed measuring unique preferences or strategies between individuals, rather than being examined by variables with absolute rightness (e.g., accuracy) as in other psychological paradigms (e.g., is this test item a ‘new’ one or an ‘old’ one in the recognition memory paradigm).In gambling paradigms, the IGT (Bechara et al., 1994) measured the pattern of deck selections associated with potential positive and negative outcomes, and subjects were required to identify the advantageous deck as the test progressed based on trial-by-trial learning. Bechara et al. (1998) used the IGT to reveal that patients with damage in the ventromedial PFC region make fewer advantageous deck selections compared with control subjects. Importantly, the impairment on IGT performance was selectively linked to lesions in the ventromedial PFC region, where patients with dorsolateral PFC lesions had intact performance on the IGT, but demonstrated deficits on working memory instead. Evidence from neuroimaging studies employing the IGT also gave convergent evidence showing that the orbital part of the PFC (or OFC region) was activated consistently during the IGT (Ernst et al., 2002), and also identified the level of neural activity in the ventromedial PFC region significantly correlated with IGT performance (Northoff et al., 2006). These results established a robust link between the ventromedial part of the PFC region and the gambling behaviours measured by the IGT.

In gambling paradigms, distinct behaviours were observed when processing positive and negative outcomes. Patients with damage to the OFC region had impairments on maximizing rewards and minimizing losses, as well as showing deficits in social interactions and emotional processing characterized by inappropriate or irresponsible behaviours (Rolls, Hornak, Wade, & McGrath, 1994). This raised a possible question regarding the functional role of the OFC region in processing representations of positive and negative values. A possible explanation of this unique role the OFC region plays in domain-specific risky behaviours was evident by its anatomical connections with other brain regions, where the OFC region received information from all sensory modalities (Rolls, Critchley, Browning, Hemadi, & Lenard, 1999). Previous functional neuroimaging studies have shown that activations in the medial OFC region were associated with processing monetary reward, increasing satiation whilst eating chocolate, exposure to pleasant smell and touch, happy autobiographical episodes, beautiful paintings and successfully processing jokes. On the other hand, the lateral OFC region was found to associate with monetary punishment, increasing aversion whilst eating chocolate, being exposed to unpleasant smell and touch, and sad autobiographical episodes (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Small, Zatorre, Dagher, Evans, Jones-Gotman, 2001; Rolls, O'Doherty, Kringelbach, Francis, Bowtell, & McGlone, 2003; Markowitsch, Vandekerckhove, Lanfermann, & Russ, 2003; Kawabata & Zeki, 2004; Goel & Dolan, 2001). A meta-analysis based on fMRI literature investigating the functional role of the human OFC region proposed a medial versus lateral differentiation, where the medial OFC region was associated with activations relating to monitoring reward, and the lateral OFC region was associated with activations related to punishment (see Kringelbach and Rolls, 2004). Therefore, it seems necessary to distinguish the relationship between different sub-regions in the PFC area along the medial-lateral axis and the cognitive behaviours associated with processing rewards and punishments.

In the current gambling test, we modified the Cups test (Levin et al., 2007; Weller et al., 2007) and investigated risk-taking behaviours to potential gains and losses at varying levels of EVs separately. Xue et al. (2009) employed the Cups test during fMRI and found that subjects' risk preference (risk rate to EQEV trials) was positively correlated with the level of ventromedial PFC activation in the win versus lose contrast. Moreover, fMRI result also revealed that the activation in the dorsomedial PFC region was stronger when subjects made risky decisions compared with making safe decisions. A similar dorsomedial PFC activation was also observed in studies using the IGT when subjects choose the risky option comparing with choosing the safe option (Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005; Tanabe, Thompson, Claus, Dalwani, Hutchison, & Banish, 2007). These results implied that the ventral part of the medial PFC region was involved with functions relating to 'processing the representation of values', whereas the dorsal part of the medial PFC region was associated with cognitive processes relating to 'make risk-taking actions or not'. When it comes to risky decisions, TD people tended to take risks when it is advantageous and to play it safe when it is disadvantageous, e.g., sensitivity to EVs in Levin et al. (2007). This suggested that risk-taking actions to different scenarios (e.g., RA, RD situations) might involve with different cognitive processes. In the gambling test here, we followed the rationale established by the Cups test, and presented subjects two competing options varying in EVs, where some trials were risk advantageous (RA), some trials were risk disadvantageous (RD), and some trials had equal expected values (EQEV). In the previous section, baseline performances established by 107 healthy TD subjects showed distinct relationships between risk rate and repetitiveness in the win and the lose conditions. In the current section, we focus on identifying the neural correlates that associated with risk rate and repetitiveness under different experimental conditions. To achieve this, we examined the link between the GM volumes in different PFC sub-regions and risk-taking behaviours to RA, RD and EQEV trials in the win and the loss conditions separately. Based on the evidences demonstrated by previous functional imaging studies, we hypothesised that the neural correlates in different PFC sub-regions would be associated with different risk-taking behaviours. In the first step, we analysed the overall risk rate and the overall repetitiveness in the win and the loss conditions. For the neural correlates associated with risk rate, based on the functional distinction between medial vs. lateral OFC and processes relating to rewards vs. punishments, we hypothesised that the overall risk rate in the win condition would correlate with the medial OFC region, whereas the overall risk rate in the lose condition would correlate with the lateral OFC region. For the neural correlates associated with repetitiveness, we hypothesised that the overall repetitiveness in the win and the loss condition would both correlate with the dorsomedial PFC region. In the second step, the neural correlates that associated with risk rate and repetitiveness to varying levels of EVs were investigated. Furthermore, we also investigated the neural correlates associated with the cognitive bias of framing effect (Tversky and Kahneman, 1981), which was evident in the original Cups test, as well as in the baseline performance established by the TD group in previous section. Previous fMRI studies investigating framing effect revealed that activation in the lateral OFC region modulated the framing effect using the IGT (Windmann et al., 2006), and a modified version of the 'Asian disease problem' (Zheng, Wang, & Zhu, 2010). These functional findings implied that the lateral OFC region was involved with biasing a weighting mechanism between rewards and punishments. As a result, we hypothesised that the size of the framing effect in the gambling test would correlate with the GM volume in the lateral OFC region.

3.6 Behavioural and VBM result of the TD sub-group

Behavioural investigation into the gambling test

The behavioural part of the result in the TD sub-group were summarised in Table 3.2.

Table 3.2. The mean and standard deviations of risk rate, repetitiveness, and reaction time (msec.) overall, and to RA, EQEV, RD trials in the win and the loss conditions of the TD sub-group were reported separately.

Condition	Variable	EV	mean	SD
Win				
	Risk rate			
		Overall	0.42	0.20
		RA	0.69	0.25
		EQEV	0.39	0.26
		RD	0.15	0.19
	Repetitiveness			
		Overall	0.67	0.18
		RA	0.77	0.24
		EQEV	0.60	0.23
		RD	0.71	0.20
	Reaction time (msec.)			
		Overall	1475.7	577.8
Loss				
	Risk rate			
		Overall	0.51	0.20
		RA	0.69	0.23
		EQEV	0.50	0.24
		RD	0.33	0.27
	Repetitiveness			
		Overall	0.58	0.22
		RA	0.66	0.22
		EQEV	0.58	0.23
		RD	0.60	0.24
	Reaction time (msec.)			
		Overall	1518.1	684.4

Risk rate

To test the sphericity of the EV variable, Mauchly's test showed that the assumption of sphericity had been violated (χ^2 (2)=53.309, p<0.00), and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity

(ε=0.629). However, the condition x EV interaction has met the assumption of sphericity (χ^2 (2)=4.287, p=0.117), so no correction of the F-ratios for the interaction effect. Repeated measures ANOVA of risk rate revealed a significant main effect of condition (F(1,122)=6.530, p=0.013), where the TD sub-group had significantly higher likelihood to make risky decisions in the loss condition than in the win condition. Repeated measures ANOVA also identified a significant main effect of EVs (F(1.259, 114.130)=164.016, p<0.001), and post-hoc test using Bonferroni correction demonstrated that the likelihood to make risky decisions was in the RA>EQEV>RD order (all pairwise comparison p<0.001). In addition, repeated measures ANOVA found a significant condition x EV interaction (F(2,122)=18.311, p<0.001). Follow-up analysis showed that the interaction was driven by more risk-taking behaviours to EQEV and RD trials in the lose condition than in the win condition, but risk rate to RA trials was comparable between the win and the lose condition.

Repetitiveness

Mauchly's test of the EV variable first found that the assumption of sphericity was met (χ^2 (2)=0.363, p=0.834), as well as the condition x EV interaction (χ^2 (2)=3.704, p=0.157). Therefore, no correct for the degrees of freedom of the F-ratios was required. Repeated measures ANOVA on repetitiveness revealed a significant main effect of condition (F(1,122)=9.612, p=0.003, where the TD sub-group showed significantly higher repetitiveness in the win condition than in the lose condition. Repeated measures ANOVA also revealed a significant main effect of EVs (F(2,122)=18.839, p<0.001), and post-hoc test using Bonferroni correction confirmed that the level of repetitiveness on risk-taking behaviours was in the

RA>RD>EQEV order (all pairwise comparisons $p<0.05$). Nevertheless, repeated measures ANOVA did not find a significant condition x EV interaction ($F(2,122)=2.905$, $p=0.059$).

Reaction time

Paired t test did not find a significant difference between reaction time in the win and the lose conditions ($t(62)=-0.723$, $p=0.472$).

Correlation analysis

The same procedure was conducted as the analysis in the TD group. In the first approach, correlation analysis did not find a significant relationship between risk rate in the win and the lose condition (r_s (62)=0.010, $p=0.936$). The analysis identified a positive significant correlation between repetitiveness in the win and the loss conditions (r_s (62)=0.448, $p<0.001$). A positive significant correlation between reaction time in the win and the loss conditions was also observed (r_s (62)=0.843, $p<0.001$). In the second approach, between-variable correlation analysis revealed a negative significant relationship between risk rate and repetitiveness in the win condition (r_s (62)=-0.495, $p<0.001$). No significant correlations were found between risk rate and reaction time (r_s (62)=-0.022, $p=0.863$), neither as between repetitiveness and reaction time (r_s (62)=0.125, $p=0.333$) in the win condition. On the other hand, correlation analysis on the between-variable effect in the lose condition did not find any significant correlations between risk rate and reaction time (r_s (62)=-0.202, $p=0.115$), between risk rate and repetitiveness (r_s (62)=0.028, $p=0.828$), and between repetitiveness and reaction time (r_s (62)=0.074, $p=0.569$).

VBM investigation into the gambling test

For VBM regression analysis, we first examined the neural correlates that were associated with the overall risk rate and the overall repetitiveness in each domain (see Table 3.3 for summary, and Figure 3.2 for illustration). Next, we inputted the variable under each condition (e.g., risk rate and repetitiveness to RA, EQEV, RD trials in the win and the lose conditions respectively) as covariates-of-interest to the regression model to explore the neural correlates that associated with the risk-taking behaviours under different conditions. The observed GM cluster that associated with risk rate and repetitiveness to varying levels of EVs are summarised in Table 3.4, and Figure 3.3, for illustration.

Table 3.3. The VBM result of the gambling test (part 1). The observed GM clusters that associated with the overall risk rate, the overall repetitiveness in the win and the loss conditions were reported, along with the peak MNI coordinate, the approximate BA region, and the ROI for small volume correction using hypothesis-testing approach based on previous relating fMRI literature.

		p<0.001, uncorrected				Small Volume Correction (FWE<0.05)					
		Whole brain analysis				AAL_Medial_Orbital		AAL_Inferior_Orbital		AAL_Superior_Medial	
		k	t	MNI	BA	p	MNI	p	MNI	p	MNI
Overall risk rate											
	Win condition	2	3.34	[14, 39, -8]	BA10	0.046	[14, 39, -8]				
	Loss condition	12	3.51	[23, 21, -9]	BA47						
		11	3.35	[51, 24, -9]	BA47						
		2	3.33	[44, 18, -6]	BA47						
Overall repetitiveness											
	Win condition	130	4.21	[-2, 50, 28]	BA9					0.014	[-2, 50, 28]
	loss condition	40	4.02	[-2, 68, 15]	BA10					0.024	[-2, 68, 15]
		13	3.62	[38, 32, -9]	BA47			0.043	[38, 32, -9]		
		20	3.47	[2, 50, 21]	BA9						

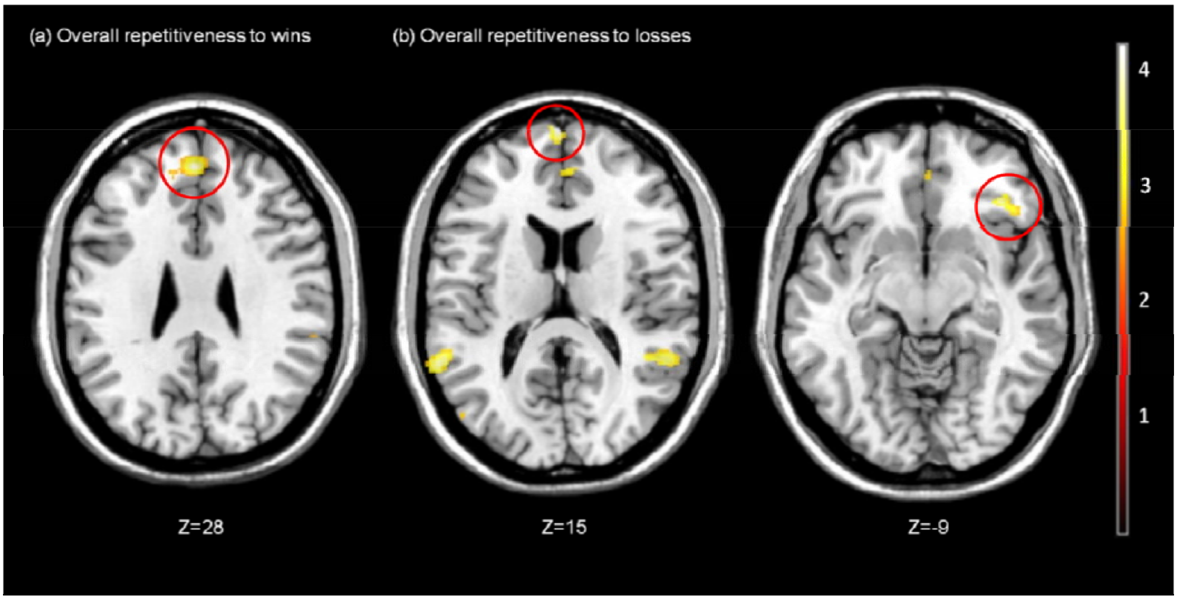


Figure 3.2. The depiction of the GM volume that significantly correlated with the variables in the gambling test. (a) The overall repetitiveness in the win condition was positively correlated with a GM cluster located in the dorsomedial PFC region. (b) The overall repetitiveness in the loss condition was positively correlated with a GM cluster in the dorsomedial PFC region (left side of the panel b), as well as a GM cluster in the lateral OFC region (right side of the panel b).

Overall risk rate and overall repetitiveness between domains

Overall risk rate

VBM regression analysis did not find a significant relationship between the overall risk rate in the win condition and any PFC region, neither as in the loss condition.

Overall repetitiveness

In the win condition, VBM regression analysis identified a positive significant correlation between the overall repetitiveness and the GM volume in the dorsomedial PFC region located in BA9 (peak MNI: -2, 50, 28; SVC: AAL_Frontal_Superior_Medial_Left, p=0.014). On the other hand, in the loss condition, VBM regression analysis identified a positive significant correlation between the overall repetitiveness and the GM volume in the dorsomedial PFC region located in BA10 (peak MNI: -2, 68, 15; SVC: AAL_Frontal_Superior_Medial_Left, p=0.024) and the GM volume in lateral OFC region located in BA47 (peak MNI: 38, 32, -9; SVC: AAL_Frontal_Inferior_Orbital_R, p=0.043).

Risk rate and repetitiveness to varying levels of EVs

Risk rate

In the win condition, VBM regression analysis revealed a positive significant correlation between risk rate to RA trials and the GM volume in the dorsomedial PFC region located in BA9 (peak MNI: -6, 50, 19; SVC: AAL_Frontal_Superior_Medial_Left, p=0.008). The analysis did not find any GM volume in the PFC region that significantly correlated with risk rate to EQEV and RD trials. In the loss condition, VBM regression analysis revealed a positive significant correlation between risk rate to RA trials and the GM volume in lateral OFC region located in BA47 (peak MNI: 47, 27, -15; SVC: AAL_Frontal_Inferior_Orbital_R, p=0.025). Nevertheless, the analysis did not find any significant correlations between risk rate to EQEV and any PFC region, neither as risk rate to RD trials and any PFC region.

Repetitiveness

In the win condition, no significant relationships were found between any PFC region and repetitiveness to RA, EQEV and RD trials. On the other hand, in the lose condition, VBM regression analysis found a positive significant correlation between repetitiveness to RA trials and the GM volume in the medial OFC region located in BA11 (peak MNI: 3, 42, -14; AAL_Frontal_Medial_Orbital_Right, p=0.028), and the GM volume in the dorsomedial PFC region located in BA10 (peak MNI: -2, 68, 15; SVC: AAL_Frontal_Superior_Medial_Left, p=0.019). No significant correlations were found between any PFC region and repetitiveness to EQEV and to RD trials.

Table 3.4. The VBM result of the gambling test (part 2). The observed GM clusters that associated with risk rate, repetitiveness to varying levels of EVs in the win and the loss conditions were reported, along with the peak MNI coordinate, the approximate BA region, and the ROI for small volume correction using hypothesis-testing approach based on previous related fMRI literature.

	p<0.001, uncorrected				Small Volume Correction (FWE<0.05)					
	Whole brain analysis				AAL_Medial_Orbital		AAL_Inferior_Orbital		AAL_Superior_Medial	
	k	t	MNI	BA	p	MNI	p	MNI	p	MNI
Risk rate										
Win condition										
RA	175	4.42	[-6, 50, 19]	BA9					0.008	[-6, 50, 19]
	53	3.61	[9, 50, 13]	BA10						
	3	3.30	[14, 39, -8]	BA10	0.051	[14, 39, -8]				
EQEV	1	3.33	[14, 39, -8]	BA10	0.048	[14, 39, -8]				
RD	18	3.38	[-5, 24, -21]	BA11						
Loss condition										
RA	97	3.83	[47, 27, -15]	BA47			0.025	[47, 27, -15]		
EQEV										
RD										
Repetitiveness										
Win condition										
RA	14	3.41	[0, 50, 31]	BA9						
EQEV										
RD	14	3.43	[-8, 50, 18]	BA9						

Loss condition										
	RA	138	4.25	[6, 42, -17]	BA11	0.028	[3, 42, -14]				
		31	4.10	[-2, 68, 15]	BA10					0.019	[-2, 68, 15]
		36	3.53	[33, 59, 3]	BA10						
		41	3.52	[3, 51, 2]	BA10						
	EQEV	9	3.53	[39, 35, -9]	BA47			0.053	[39, 35, -9]		
	RD	11	3.52	[38, 32, -9]	BA47			0.055	[38, 32, -9]		

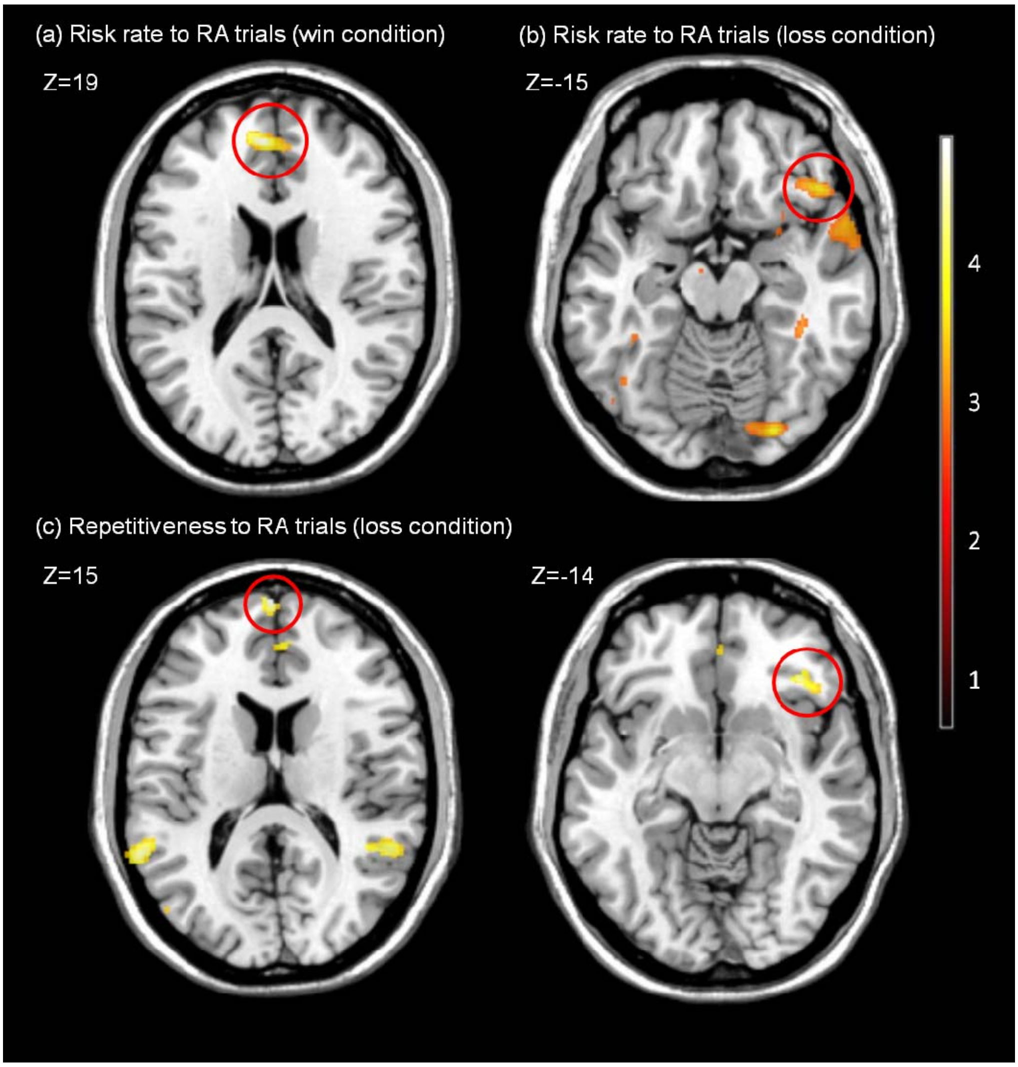


Figure 3.3. The depiction of the GM volume that significantly correlated with variables in the gambling test. (a) Risk rate to RA trials in the win condition was positively correlated with a GM cluster located in the dorsomedial PFC region. (b) Risk rate to RA trials in the lose condition was positively correlated with a GM cluster in the lateral OFC region. (c) Repetitiveness to RA trials in the lose condition was positively correlated with a GM cluster in the dorsomedial PFC region (panel c, left), as well as a GM cluster in the lateral OFC region (panel c, right).

Framing effect

VBM regression analysis identified that the size of the framing effect (the overall risk rate in the loss condition minus the overall risk rate in the win condition) was positively correlated with two GM volumes in the lateral OFC region that survived small volume corrections using the AAL_Frontal_Inferior_Orbital_Right ROI (peak MNI: 32, 24, -14, p=0.01; peak MNI: 41, 29, -21, p=0.016) (see Figure 3.4).

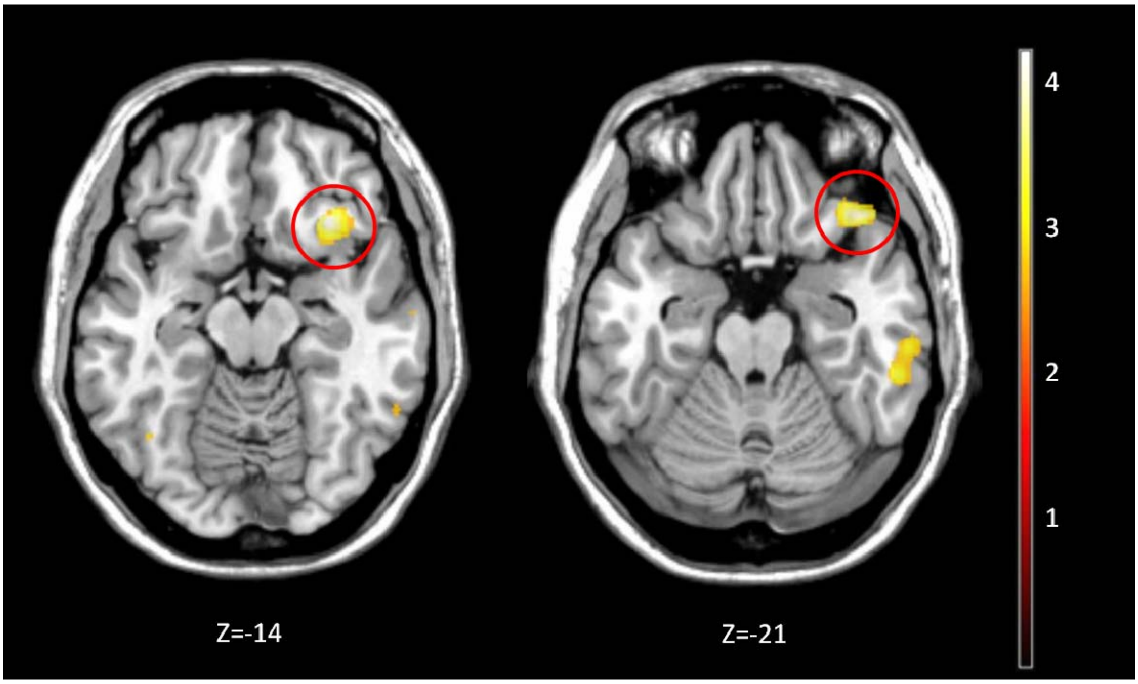


Figure 3.4. The size of the framing effect was positively correlated with two GM volumes in the lateral OFC region.

3.7 Discussion of the VBM result in the TD sub-group

The behavioural part of the result identified consistent findings of risk rate, repetitiveness and reaction time in the baseline performance established by the TD group. Repeated measures ANOVA of risk rate demonstrated that the TD sub-group had a higher propensity to take risks in the lose condition than the win condition, and showed sensitivity to manipulations to EVs. Analysis of repetitiveness revealed that the TD sub-group had higher repetitive behaviours in the win condition than in the loss condition, and the repetitive pattern to trials varying in EVs was in a RA>RD>EQEV order. No significant difference in reaction time was observed, which indicated that the TD sub-group spent comparable time evaluating risk-taking actions between the win and the loss conditions. Importantly, correlation analysis of the within-variable effect did not find a significant relationship between risk rate between the win and the loss conditions, yet a positive significant relationship was identified between repetitiveness in the win and the lose conditions. Together the behavioural performance demonstrated that the TD sub-group: 1) were sensitive to manipulations to EVs; 2) took more risks to losses than to wins and showed a framing effect; 3) demonstrated a potential differentiation on risk rate between domains, yet showed a correlation between the repetitive behaviours to wins and to losses.

VBM regression analysis was conducted in two stages. In the first stage, VBM regression analysis of the overall risk rate aimed at testing the lateral versus medial dissociation in the OFC region. In the win condition, although the overall risk rate to wins was positively correlated with the GM volume in the medial OFC region, the GM cluster that survived FWE correction was too small to meet the exclusion criterion ($k<10$). Nevertheless, this weak association was consistent with proposed function role of the medial OFC played in reward processing (Kringelbach and Rolls, 2004). On the other hand, VBM regression analysis in the lose condition found no significant correlation between the overall risk rate and the lateral OFC region. Still, it is important to note that several GM clusters located in the BA47 region were found to positively correlate with the overall risk rate to losses when using a lenient $p<0.001$ uncorrected threshold. Together the examination of the medial vs. lateral dissociation in the OFC region between the risk-taking behaviours associated with processing potential rewards vs. punishments failed to observe a reliable link using structural-based analyses.

The repetitiveness variable we calculated measured the response pattern of risk-taking actions, and analysis of the overall repetitiveness aimed at examining the link between the degree of repetitive actions whilst gambling and the regional GM volumes in the dorsomedial PFC region. VBM regression analysis of the overall repetitiveness revealed a positive significant relationship between the GM volume in the dorsomedial PFC region located in BA9 and the overall repetitiveness to both wins and to losses. This indicated that TD subjects with larger GM volumes in the dorsomedial PFC tended to choose the same options more repetitively regardless of facing potential gains or losses, which was consistent with the positive significant correlation identified at the behavioural level. It is interesting to note that the GM cluster in BA9 (peak MNI: -2, 68, 15) correlated with the overall repetitiveness in the lose condition, which located closely to the GM cluster correlated with the overall repetitiveness in the win condition (peak MNI: -2, 50, 28). Nevertheless, small volume correction using the peak MNI coordinates: -2, 50, 28 as the centre with 5 mm radius revealed that the two GM clusters in the dorsomedial PFC region were not the same GM cluster (FWE $p>0.05$). In a meta-analysis investigating the functional role of the rostral PFC region, Gilbert, Spengler, Simons, Steele, Lawrie, Frith, and Burgess (2006) demonstrated an anterior versus posterior dissociation along the medial line, where the anterior medial PFC region was associated with multitasking, and the posterior medial PFC region was associated with mentalizing. It is possible that the posterior medial PFC, a part of the social cognition network (Frith & Frith, 1999), is involved with more the affective aspect of cognitions, and this emotional regulation contributed to the repetitive behaviours following the 'win-stay' principle to reward expectation. On the other hand, the anterior medial PFC is involved with the guidance of performance, a relatively more rational aspect of cognitions. This rational consideration might contribute to the repetitive behaviours following the 'lose-shift' principle to adapt or change the routine actions in order to avoid potential punishments. In addition, VBM regression analysis of the overall repetitiveness in the loss condition also found a positive correlation with the GM volume in the lateral OFC region located in BA47, which showed that the overall repetitiveness to losses was positively correlated with a cortical region proposed to associate with processing punishment (Kringelbach and Rolls, 2004). It has been showen that the lateral OFC region was involved with a range of cognitive functions, including in the reversal-learning paradigm. A key aspect of reversal-learning was to switch from an existing association, via an overriding process, to a new alternative option due to a change in feedback contingency. Fellows and Farah (2003) used a reversal-learning paradigm and found that patients with lesions to the ventral PFC region had impairments in reversal-learning performance. In order to disentangle the complex function associated with this complex process, Hampshire, Chaudry, Owen, and Roberts (2012) implemented a reversal-learning test to examine the contribution of different PFC sub-regions during the following time points: processing negative feedback, initiation of new search, reversal, and switching from one object to another. Functional imaging result revealed that both lateral OFC and lateral PFC regions responded at the point of reversal. Critically, only the lateral OFC region activated at the time of the switch occurred following contingency reversal, whereas the lateral PFC region activated in an indistinguishable way during all switching points. The 'win-stay, lose-shift' principle in gambling implied an universal tendency to change when experiencing a negative association between punishment and a particular option. Under that circumstance, subjects would reverse their strategy to the negatively associated option based on the feedback, and switch to other alternative options. Therefore, this implied that the variables measuring risk-taking actions (e.g., risk rate, repetitiveness) were like two sides of the same coin, where the lateral OFC region could be associated with a 'change of behaviours', as well as processing punishment. Further evidence was provided by Liu, Powell, Wang, Gold, Corby, and Joseph (2007), where lateral OFC was not recruited when negative outcomes arose in a gambling test, but arose at a later time when an urge was overridden based on negative feedback. Taken together, the repetitiveness variable provides another perspective to view risk-taking behaviours other than the risk rate, and further suggests an 'action-based' interpretation replying on different PFC sub-regions including the dorsomedial PFC and the lateral OFC regions.

In the second step of the VMB analysis, we further analysed the function-structure relationship between risk-taking behaviours to varying levels of EVs and the regional GM volume in different PFC sub-regions. VBM analysis found a positive significant correlation between risk rate to RA trials and the GM volume in the dorsomedial PFC region located in BA9 (peak MNI: -6, 50, 19), a region close to the identified GM cluster that associated with the overall repetitiveness to wins (peak MNI: -2, 50, 28). In the behavioural part of the result, the propensity to make risky decisions was the highest to RA trials, and a significant relationship between the overall risk rate and the overall repetitiveness was only evident in the win condition.

Given that repetitive behaviour was more prominent when it comes to situations that favoured risk-taking decisions, it is possible that the observed correlation here demonstrated a link between evaluations of positive valence and enhanced repetitive behaviours. In the loss condition, on the other hand, VBM regression analysis found a positive significant correlation between risk rate to RA trials and the GM volume in the lateral OFC region located in BA47. This indicated that the bigger size of the lateral OFC region, the higher propensity for TD subjects chose to avoid punishments under situations favouring risk-taking actions, which was consistent with the proposed role of the lateral OFC played in evaluating potential punishments (Kringelbach and Rolls, 2004). Furthermore, as discussed earlier, brain activity in the lateral OFC region has been found to activate during the switch of existed association due to contingency reversal, as well as an urge to override existed behaviour pattern due to negative feedback. The behavioural part of the result demonstrated that risk rate was the highest to RA trials, which indicated that the 'urge to change behaviour' was most prominent in the situations that favoured risk-taking actions. As a result, the behavioural and VBM results together suggest a possible link between the size of different PFC sub-regions and the potential mechanism behind the 'win-stay, lose-shift' principle of risk-taking behaviours, where the likelihood to take risks to potential wins was associated with repetitive actions, and the likelihood to take risks to potential losses was associated with change of actions. Furthermore, the analysis of risk rate to varying levels of EVs highlighted a possible distinction between risk-taking actions in scenarios specifically favouring risk-taking actions, which provided further insights on the evaluation processes to potential rewards and punishments in the gambling paradigm.

VBM regression analysis of repetitiveness in the win condition did not identify any significant relationships between the repetitive behaviours to varying levels of

EVs and any PFC region. On the other hand, in the lose condition, repetitiveness to RA trials was found to positively correlate with GM volumes in the dorsomedial PFC region located in BA10 (peak MNI: -2, 68, 15), the same GM cluster that positively correlated with the overall repetitiveness to losses (peak MNI: -2, 68, 15). It is important to note that repetitiveness to RA trials did not find to correlate with the GM volumes in the lateral OFC region as the overall repetitiveness to losses did. It is therefore consistent with a proposed role for the dorsomedial PFC region in 'making the action' per se. Interestingly, VBM regression analysis also identified a positive relationship between repetitiveness to RA trials to losses and the GM volumes in the medial OFC region, an area frequently linked to reward processing. The observed association suggested that the repetitiveness variable we calculated measured cognitive behaviours other than processing positive or negative valence. Given that repetitiveness was the highest to RA trials in the loss condition, it is possible that a risk-aversive 'action' under situations that favoured risky decisions was associated with the similar affectively rewaring processes as evaluating outcomes in positive valence.

Lastly, VBM regression analysis revealed that the size of framing effect was positively correlated with the GM volume in the lateral OFC region located in BA47. To examine the social aspect of framing effect, Zheng et al. (2010) asked subjects to administer a modified 'Asian disease problem' involving a large group size (600 endangered people) and a small group size (6 endangered people). Their result showed that the positive frame elicited greater activation in the lateral OFC region (peak MNI: 33, 29, -8) in the large group context, a location very close to the identified GM cluster in BA47 in our VBM finding. Furthermore, brain activities in the lateral OFC have been shown to correlate with behaviours relating to risk aversion (Christopoulos, Tobler, Bossaerts, Dolan, & Schultz., 2009), and interruption to this brain structure results in changes of risk attitude (Fecteau, Knoch, Fregni, Sultani, Boggio, & Pascual-Leone, 2007; Knoch et al., 2006). As a result, this lateral OFC region seems to play an important role in a cognitive control mechanism specifically for regulating risk-taking impulses.

3.8 Atypical performance of risk-taking behaviour to potential wins vs. losses in ASD subjects

Adherence to restricted, repetitive, and stereotyped behaviours is one of the core symptoms of ASD, along with social and communication difficulties. The classes of repetitive mannerisms are characterised by high frequency, repetition in an invariant manner, and desire for sameness in the environment (Kanner, 1943). The repetitive behaviours including preoccupation with restricted interests and non-functional routines or rituals, which is described by the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; *DSM-IV*; American Psychiatric Association, 1994), has been characterised as 'desire for sameness to a marked degree' (Prior & Macmillan, 1973). Turner (1999) described the repetitive symptoms, including insistence on the maintenance of sameness and circumscribed interests, as 'higher-level' repetitive behaviours, compared with 'lower-level' repetitive motor actions. Previous studies of this repetitive mannerism reported a unitary repetitive factor amongst individuals with ASD (South, Ozonoff, & Mcmahon, 2005), and an 'insistence on sameness' factor emerged reliably across studies of children with ASD (Leekam, Prior, & Uljarevic, 2011). However, the underlying cognitive process underneath these repetitive behaviours observed in ASD individuals is not yet clear.

One of the theories raises a possibility that the poor regulation or impaired control mechanism of repetitive behaviours may be associated with cognitive inflexibility or executive dysfunction (see Hill, 2004; Kenworthy, Yerys, Anthony, & Wallace, 2008; Geurts, Corbett, & Solomon, 2009 for review). Studies of cognitive flexibility using gambling paradigms provide opportunities to measure individual's unique response pattern in terms of risk-taking behaviours. For example, De Martino et al. (2008) used a gambling test that requited subjects to make decisions by comparing a sure and a gamble option with balanced expected value under gain and loss frames. The result revealed that adults with ASD demonstrated a reduced framing effect, compared with the control group, which demonstrated significantly more similar risk-taking behaviours between the win and the loss frames. This less susceptibility to framing effect suggested a failure to integrate contextual information between different domains. Coincidently, the medial PFC region has been shown to be responsible for integrating cognitive and emotional information, and previous neuroimaging studies reported that people with ASD had structural abnormalities in the medial PFC region (Waiter et al., 2004; Courchesne, Campell, & Solso, 2011). Based on previous studies using the Cups test showed that patients with ventromedial PFC lesions demonstrated insensitivity the manipulation of varying levels of EVs (Levin et al., 2007; Weller et al., 2007), we hypothesised that ASD adults would demonstrate similar insensitivity to EVs between the win and the loss condition in the gambling test here. We examined the susceptibility to the framing effect between the TD and the ASD groups as reported in De Martino et al. (2008), and expected to find that adults with ASD would show atypical susceptibility to the switch of frames compared with the baseline performance established by the TD group.

Another topic that raised increasing attention in studies using gambling paradigms to investigate the inflexible, repetitive behaviours among ASD subjects was the change of response pattern over time. For example, Johnson, Yechiam, Murphy, Queller, and Stout (2006) used the IGT to evaluate risk-taking behaviours in adolescents with ASD, and reported no deficits in advantageous deck selection compared with the control group. However, the ASD group made shorter consecutive runs of selecting the advantageous deck than the control group, which suggested a constant shift between the four alternative decks amongst ASD subjects. Furthermore, despite similar proportions of advantageous deck selection between groups on average, Johnson et al. (2006) found a trend of increasing between-group differences in proportion of advantageous deck selection as the IGT progressed, where ASD subjects learnt the advantageous deck more slowly. Similar finding was demonstrated by Yechiam, Arshavsky, Shamay-tsoory, Yaniv, and Aharon (2010), which revealed that both ASD and control groups learnt to make advantageous deck selection over time, yet a significant group x test block interaction indicated that the adaptive learning process of advantageous deck selection was significantly slower in the ASD group than in the control group. A recent study by South et al. (2014) used the IGT to study decision-making in adolescents with ASD, and also found a significant group x block interaction driven by more frequent and a longer runs of the advantageous deck selection over time in the ASD group, compared with the control group. Taken together, previous IGT studies reveal a potential dynamic change of adaptive learning style to risk-taking actions over time. This intrigued us to examine if a similar adaptive learning pattern could be observed in the gambling test here. As a result, we examined the change of risk-taking behaviours along a temporal scale by dividing the performance into an early stage (the first half of all the trials) and a late stage (the second half of all the trials). Based on previous findings using the IGT, we hypothesised that ASD subjects would demonstrate atypical risk-taking behaviours compared with TD subjects as the test progressed.

3.9 Behavioural result between the ASD and the TD groups

Between-group effect

Experimental variables including risk rate, repetitiveness, and reaction time were entered into a repeated measures ANOVA with condition (win vs. loss), EVs (RA, EQEV, RD) as within-subject factors, and group (TD vs. ASD) as between-subject factor. The behavioural result of the ASD group, as well as the baseline performance in the TD group, were summarised in Table 3.5.

Table 3.5 The mean and standard deviations of risk rate, repetitiveness, and reaction time (msec.) overall, and to RA, EQEV, RD trials in the win and the loss conditions were reported separately for the TD and the ASD groups.

			TD group		ASD group	
Condition	Variable	EV	mean	SD	mean	SD
Win						
	Risk rate					
		Overall	0.42	0.20	0.36	0.23
		RA	0.71	0.26	0.64	0.34
		EQEV	0.39	0.28	0.30	0.31
		RD	0.15	0.20	0.12	0.20
	Repetitiveness					
		Overall	0.69	0.18	0.52	0.19
		RA	0.78	0.24	0.86	0.22
		EQEV	0.62	0.24	0.78	0.20
		RD	0.73	0.20	0.80	0.21
	Reaction times (msec.)					
		Overall	1384.4	494.4	1699.2	500.3
Loss						
	Risk rate					
		Overall	0.52	0.21	0.52	0.19
		RA	0.72	0.24	0.76	0.24
		EQEV	0.49	0.26	0.50	0.28
		RD	0.33	0.28	0.30	0.27
	Repetitiveness					
		Overall	0.59	0.22	0.66	0.27
		RA	0.66	0.24	0.70	0.28
		EQEV	0.58	0.25	0.59	0.29
		RD	0.63	0.24	0.68	0.30
	Reaction times (msec.)					
		Overall	1472.8	646.8	1795.6	651.6

Risk rate

First, test of sphericity first revealed that the assumption of sphericity had been violated on the EV factor (Mauchly's test χ^2 (2)=92.6409, p<0.001), and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon=0.672$). However, the condition x EV interaction has met the assumption of sphericity (χ^2 (2)=0.620, p=0.734), so there was no correction of the F-ratios for the interaction effect. Repeated measures ANOVA did not find a significant main effect of group (F(1,139)=0.890, p=0.347). The analysis identified a significant main effect of condition (F(1,139)=22.059, p<0.001) and of EV (F(2,278)=243.018, p<0.001), where subjects made significantly more risk-taking behaviours in the loss condition than in the win condition, and the propensity to take risks was in the RA>EQEV>RD order (all pairwise comparison p<0.001 using Bonferroni correction). No significant condition x group (F(1,139)=1.349, p=0.247), or EV x group interactions (F(2,278)=0.186, p=0.830) was found. Nevertheless, a marginally significant condition x EV x group interaction (F(2,278)=2.876, p=0.058) was found, and follow-up analysis revealed that the higher propensity to take risks to RA trials in the loss condition than in the win condition was higher in the ASD group than in the TD group.

Repetitiveness

Mauchly's test on the EV variable found that the assumption of sphericity was met (χ^2 (2)=3.671, p=0.160), as well as the condition x EV interaction (χ^2 (2)=4.783, p=0.092). As a result, we did not correct for the degrees of freedom of the F-ratios. Repeated measures ANOVA found a significant main effect of group (F(1,139)=4.242, p=0.041), where the ASD group had significantly higher repetitiveness than the TD group. The analysis also identified a significant main effect of condition (F(1,139)=34.943, p<0.001) and of EV (F(2,278)=22.305, p<0.001), which showed a significantly higher degree of repetitive behaviours in the win condition than in the loss condition, and the repetitiveness was in the RA>RD>EQEV order (all pairwise comparisons p<0.05 using Bonferroni correction). No significant condition x group (F(1,139)=2.940, p=0.089), EV x group interactions (F(2,278)=0.465, p=0.629), and condition x EV x group interaction (F(2,278)=2.112, p=0.123) was found.

Reaction time

Similar to the procedure in the TD group, we collapsed the EV factor and conducted repeated measures ANOVA using condition (win vs. loss) as a within-subject factor, and group (TD vs. ASD) as a between-group factor. Repeated measures ANOVA revealed a significant main effect of group (F(1,139)=9.649, p=0.002), which showed that the ASD group made risky decisions significantly slower than the TD group in general. No significant main effect of condition (F(1,139)=3.615, p=0.059), or condition x group interaction (F(1,139)=0.007, p=0.935) was found.

Supplementary analysis

In order to compare the susceptibility to framing effect described in De Martino et al. (2006), where gambling trials had equal expected values, we analysed the framing x group interaction of risk rate to EQEV trials. The framing x group interaction on repetitiveness to EQEV trials was also examined. Repeated measures ANOVA of risk rate to EQEV trials did not find a significant framing x group interaction (F(1,139)=1.451, p=0.230). On the other hand, analysis of repetitiveness to EQEV trials found a significant framing x group interaction (F(1,139)=5.977, p=0.016). Follow-up analysis showed that the enhanced repetitiveness in the ASD group than in the TD group was significant only in the win condition (p=0.001) but not in the loss condition (p=0.797) (see Figure 3.5, for illustration).

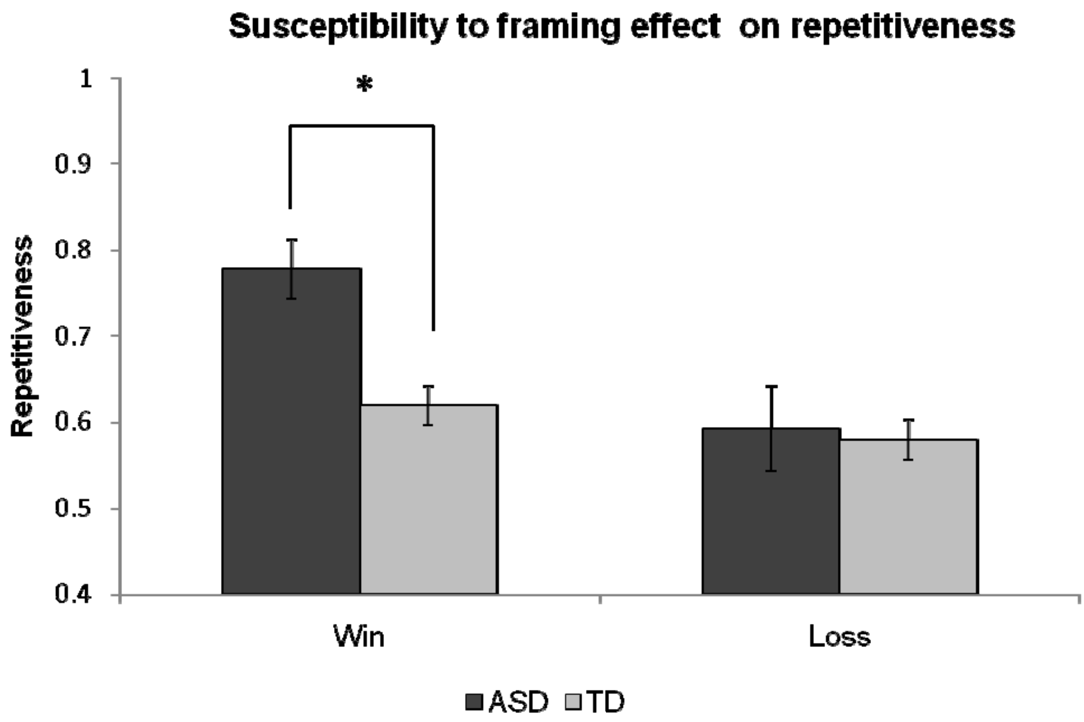


Figure 3.5. The demonstration of the significant framing x condition interaction on the repetitiveness to EQEV trials.

Adaptive learning over time

The aim of this section was to examine the change in behaviour as the test progressed by introducing an additional factor of stage, where the first half of the data were labelled as the early stage, and the second half of the data were labelled as the late stage. Repeated measures ANOVA with condition (win vs. loss), stage (early vs. late) as within-subject factors, and group (TD vs. ASD) as between-subject factor was conducted. The results of overall risk rate, overall repetitiveness, and overall reaction time, as well as the results of each variable in the early stage and the late stage were summarised in Table 3.6.

Table 3.6. The mean and standard deviations of risk rate, repetitiveness, and reaction time (msec.) in the earky and the late stages of the win and the loss conditions were reported separately for the TD and the ASD groups.

			TD group		ASD group	
Condition	Variable	Stage	mean	SD	mean	SD
Win						
	Risk rate					
		Early	0.41	0.21	0.35	0.22
		Late	0.43	0.21	0.37	0.24
	Repetitiveness					
		Early	0.75	0.16	0.84	0.17
		Late	0.77	0.16	0.87	0.18
	Reaction times (msec.)					
		Early	1625.7	622.2	2052.1	656.1
		Late	1143.0	425.5	1346.4	427.2
Loss						
	Risk rate					
		Early	0.56	0.21	0.54	0.19
		Late	0.47	0.24	0.50	0.23
	Repetitiveness					
		Early	0.69	0.18	0.71	0.21
		Late	0.70	0.18	0.76	0.21
	Reaction times (msec.)					
		Early	1709.4	781.5	2227.1	920.0
		Late	1236.1	563.4	1364.2	459.4

Risk rate

Repeated measures ANOVA of risk rate found a significant main effect of stage ($F(1,139)=6.106$, $p=0.015$), which showed that subjects had significantly more risk-taking behaviours in the early stage than in the late stage. The analysis also revealed a significant main effect of condition ($F(1,139)=22.273$, $p<0.001$), where subjects took significantly more risks in the loss condition than in the win condition.

Repeated measures ANOVA did not find a significant main effect of group ($F(1,139)=0.850$, $p=0.358$). Importantly, the analysis revealed a significant condition x stage interaction ($F(1,139)=18.827$, $p<0.001$). Follow-up analysis showed that the tendency to take fewer risk-taking actions in the late stage was higher in the loss condition than in the win condition. No significant stage x group ($F(1,139)=1.126$, $p=0.270$) and significant condition x stage x group interaction ($F(1,139)=0.794$, $p=0.375$) were found.

Repetitiveness

Repeated measures ANOVA revealed a significant main effect of stage ($F(1,139)=6.013$, $p=0.015$), where subjects responded more repetitively in the late stage than in the early stage. The analysis found a significant main effect of group ($F(1,139)=5.491$, $p=0.021$), which revealed that the ASD group had significantly higher repetitiveness than the TD group. Repeated measures ANOVA also found a significant main effect of condition ($F(1,139)=35.586$, $p<0.001$), which showed that the repetitiveness was significantly higher in the win condition than in the loss condition. Nevertheless, no significant stage x group interaction, condition x group interaction, condition x stage interaction, and condition x stage x group interaction were found (all $p>0.05$).

Reaction time

Repeated measures ANOVA on reaction time revealed a significant main effect of stage ($F(1,139)=257.764$, $p<0.001$), which showed that all subjects responded significantly slower in the early stage than in the late stage. The analysis also found a significant main effect of group ($F(1,139)=9.649$, $p=0.002$) showing ASD subjects responded significantly slower than TD subjects in general. No significant main effect of condition was found ($F(1,139)=3.615$, $p=0.059$). Repeated measures ANOVA identified a significant stage x group interaction ($F(1,139)=15.172$, $p<0.001$). Follow-up analysis revealed that the response slowness of the ASD group was higher in the early stage than in the late stage. No significant condition x group ($F(1,139)=0.007$, $p=0.935$) and condition x stage ($F(1,139)=3.004$, $p=0.085$) interactions were found. Importantly, repeated measures ANOVA found a marginal significant group x condition x stage interaction ($F(1,139)=3.819$, $p=0.053$). Follow-up analysis showed that the ASD group had response slowness in both stages of the win condition, the early stage in the loss condition, but the response speed was comparable to the TD group in the late stage of the loss condition.

Supplementary analysis

In the current gambling test, we used a block design that required all subjects to administer the win condition first, and then the loss condition. As a result, there was one major ‘switch’ of frames between the win and the loss condition in the current paradigm, where subjects needed to disengage from the scenarios of facing potential gains and changed to a mode of facing scenarios with potential losses. Behavioural results from previous sections indicated that all subjects took significant fewer risky decisions, had significantly higher repetitiveness, and a tendency towards faster response speed ($p=0.059$) in the win condition than in the loss condition. These results suggested that subjects implemented a different strategy between processing potential monetary rewards and potential monetary punishments. To investigate this ‘switch’ of frames under the block design, we conducted repeated measures ANOVA by inputting the three variables (risk rate, repetitiveness, reaction time) in the late stage of the win condition and the early stage of the loss condition, and focused on examining the group x 'switch of frames' interaction. Analysis of risk rate did not find a significant interaction ($F(1,139)=0.489$, $p=0.485$). Repeated measures ANOVA of repetitiveness identified a significant group x 'switch of frames' interaction ($F(1,139)=4.399$, $p=0.038$). Follow-up analysis showed that the enhanced repetitive behaviour amongst ASD subjects was higher in the late stage of the win condition than in the early stage of the loss condition (see Figure 3.6). Repeated measures ANOVA of reaction time also revealed a significant group x 'switch of frames' interaction ($F(1,139)=5.263$, $p=0.023$). Follow-up analysis demonstrated that the 'cost' of switching frames from win to loss was higher in the ASD group (mean difference=880.7 msec.) than in the TD group (mean difference=566.4 msec.).

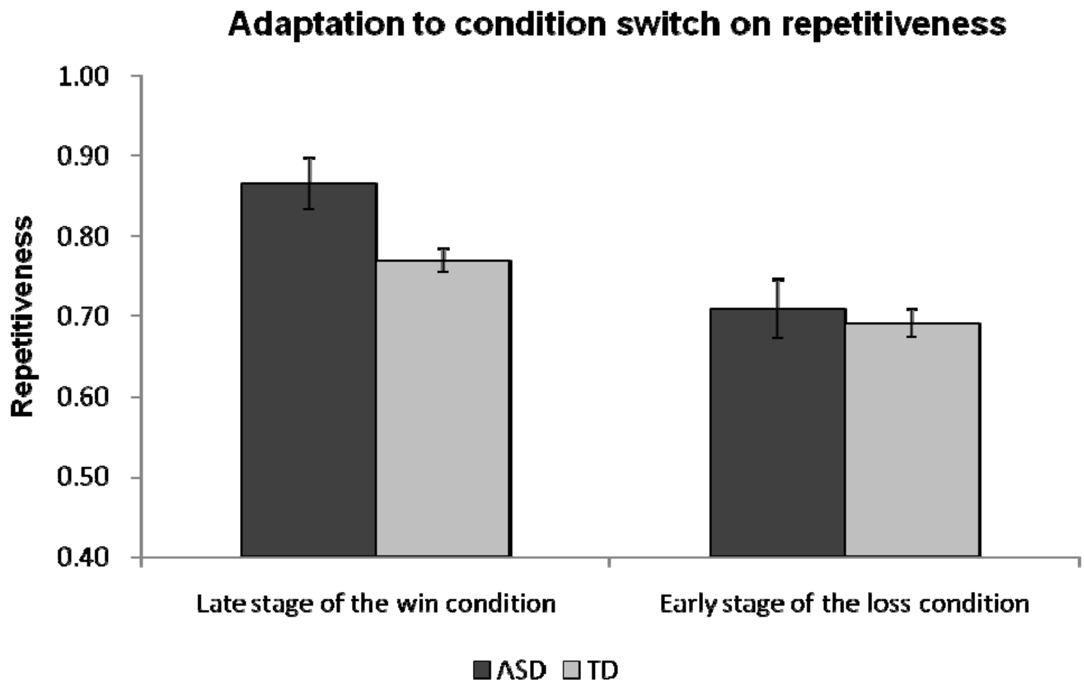


Figure 3.6. The group x ‘switch of frames’ interaction on repetitiveness showing adaptation to change of contexts.

3.10 Discussion of the behavioural result between the ASD and the TD groups

The first part of the analysis focused on examining between-group differences by comparing the risk-taking behaviours to varying levels of EVs in the win and the loss condition amongst ASD subjects to the baseline performance established by 107 TD subjects. Repeated measures ANOVA of risk rate showed that both groups revealed a sensitivity to manipulation of EVs by taking more risky decisions in a RA>EQEV>RD order. In addition, both groups revealed a framing effect by taking more risks in the loss than in the win condition. However, despite showing lower propensity to take risks in the ASD group, no significant main effect of group was found, which showed that ASD subjects did not demonstrate a significantly more risk-averse strategy in the gambling test. Analysis of the interaction identified a marginal three-way interaction. Follow-up analysis identified that framing effect to RA trials was higher in the ASD group than in the TD group, which suggested an enhanced cognitive bias to avoid potential losses under situations favouring risky decisions. Repeated measures ANOVA of repetitiveness first showed a significant condition effect, which suggested that both groups followed a ‘win-stay, lose-shift’ principle by making decisions more repetitively to wins than to losses. The analysis also identified a significant main effect of condition, where the repetitive behaviours were in a RA>RD>EQEV order in both groups. Critically, analysis of repetitiveness found a significant effect of group, where the ASD group demonstrated significantly higher repetitiveness than the TD group. This revealed that ASD subjects were more fixated on a certain response pattern than the TD group. Repeated measures ANOVA of reaction time found a significant main effect of group, showing ASD subjects responded significantly slower than TD subjects in general, which was consistent with the general slowness observed in previous ASD studies (Ozonoff, Strayer, Mcmahon, & Filloux, 1994).

In De Martino et al. (2008), a significantly smaller framing effect was observed in the ASD group than in the control group, which suggested insensitivity to context amongst ASD subjects. Critically, the trials showing a sure and a gamble options in De Martino et al. (2008) were all equal on expected values, but varying in EVs in the current gambling test. As a result, in order to examine the susceptibility to framing effect reported in De Martino et al. (2008), we focused on investigating the group x condition interaction of risk rate, repetitiveness specifically to EQEV trials. However, analysis of risk rate did not find a significant group x condition interaction. To explain this inconsistency, it is important to note the difference in experimental design between the two gambling paradigms. In De Martino et al. (2008), the win and the loss frames were intermixed with each other, whereas we used block design to separate the win and the loss condition. It is possible that the presentation of gain versus loss frames was either mixed or separated would lead to fundamental difference in the strategy implemented. For example, as ASDs are diagnosed to have enhanced repetitive mannerisms, it was intuitive to suspect that ASD subjects would be more vulnerable to a frequent switch between frames, which might subsequently result in the observed insensitivity to contextual change, or actually make it indistinguishable between frames amongst ASD subjects as reported in De Martino et al. (2008). As the marginal three-way interaction identified in risk rate in the current gambling test shows, the enhanced framing effect (taking more risks to losses than to wins) to RA trials suggested that ASD subjects tried even harder to avoid potential losses in situations favouring risk-taking actions. This highlighted a potential differentiation when analysing gambling decisions under risk-advantageous and risk-disadvantageous scenarios, where a certain ‘push’ to either side of the decision (e.g., to risk or not to risk) might provide fruitful information of the risk-taking actions between ASD individuals. On the other hand, repeated measures ANOVA found a significant group x condition interaction on repetitiveness to EQEV trials, where the ASD subjects responded more repetitively than the TD subjects only to potential wins, but not to potential losses. This finding highlighted a more rigid response strategy to potential gains implemented in ASD subjects under situations that favoured either safe or gamble actions. This interaction also suggested that when it comes to facing potential losses, ASD subjects would be willing to explore different response strategies as TD subjects, and demonstrated a domain-specific rigidness of responding, or a selectively enhanced ‘win-stay’ strategy amongst ASD subjects.

The second part of the analysis focused on the effect of 'stage' by exploring the temporal change of performance between the early stage (block1-4) and the late stage (block6-9). Repeated measures ANOVA of risk rate revealed a significant main effect of stage, where all subjects made more risk-taking actions in the early stage than in the late stage. This was consistent with the classic 'exploration vs. exploitation' dilemma in gambling paradigms, where subjects aimed at optimising their decisions based on accumulated feedback. In the current gambling test, all subjects tended to implement an exploratory strategy by making more risky decisions in the early stage, and exploited the optimised strategy by making fewer risky decisions based on their accumulated feedbacks. Furthermore, the observed condition x stage interaction indicated that the fewer risky actions effected in the late stage was more prominent in the loss condition. This implied a context-dependent exploration exploitation transaction, where subjects tended to be more risk-averse, or exploited their established strategy based on the exploration process in the early stage in an enhanced fashion when facing potential losses than to wins. Repeated measures ANOVA of repetitiveness identified a significant main effect of stage, which showed that all subjects responded more repetitively in the late stage than in the early stage. This enhanced repetitiveness in the late stage was also in line with the 'exploration – exploitation' explanation proposed earlier when examining the temporal change of risk-taking behaviours, where the exploitation process, by definition, would involve with more fixated response pattern. It is important to note that, although no significant group x stage interaction of repetitiveness was found, repetitiveness scores were higher in the ASD group than in the TD group in both early and late stages in two domains. A similar finding was reported in South et al. (2014), where results of the IGT revealed longer runs of advantageous deck selection in the ASD group than in the control group. A key difference between the pattern of deck selection in the IGT and the repetitiveness variable in the gambling test was the way to measure repetitive behaviour. In the gambling test, the repetitiveness variable represented the pattern of option selection, whereas longer runs of advantageous deck selection in the IGT (e.g., South et al., 2014) measured repetitive behaviours in a sequentially along a temporal scale. In other words, choosing the same option consecutively represented different rigid behaviour compared with always choosing the same option whenever that option occurred. Further investigation is required to disentangle the differences between ‘inflexibility to explore new options’ and ‘rigid exploitation on certain option selection strategy’, or, in everyday language, ‘I would rather not go outside of my comfort zone’ vs. ‘I’d rather stay inside of my comfort zone’. Repeated measures ANOVA of reaction time also revealed a significant main effect of stage, and the result identified that all subjects made their decisions significantly faster in the late stage than in the early stage. Importantly, repeated measures ANOVA of reaction time revealed a marginal significant three-way interaction. Follow-up analysis confirmed the interaction was driven by significant general slowness amongst ASD subjects throughout the whole win condition, the early stage of the loss condition, but the slowness became insignificant in the late stage of the loss condition. This suggested that the ASD subjects were able to compensate their response slowness, specifically when evaluating potential losses, as the test progressed. In previous studies using the IGT, temporal changes of risk-taking behaviours in the ASD group were reported, including slower advantageous deck learning and longer runs of advantageous deck selection (Johnson et al., 2006; Yechiam et al., 2010; South et al., 2014). Our finding concerning reaction time is consistent with Johnson et al. (2006) and Yechiam et al. (2010), where ASD subjects, compared with TD subjects, revealed a slower learning curve on risk-taking behaviours. Nevertheless, we have further raised a potential issue regarding different learning curves to potential wins and losses amongst ASD subjects.

In other gambling test studies investigating ASD subjects, like De Martino et al. (2008), win trials and loss trials were presented in an intermixed way, which created a certain ‘switch’ of domains between processing potential wins and losses. In our gambling test, we used a block design to separate the win and the loss conditions to enable building up a certain response strategy as the test progressed. In order to examine the sensitivity to change of context, we measured the effect of ‘switch of frames’, which was the late stage in the win condition and the early stage in the loss condition. Repeated measures ANOVA did not find a significant group x ‘switch of frames’ interaction of risk rate, but on repetitiveness instead. Follow-up analysis showed that ASD subjects responded more repetitively than TD subjects did in the late stage of the win condition, but demonstrated comparable repetitiveness as TD subjects in the early stage of the loss condition after a switch of context. This was first in line with the enhanced repetitiveness amongst ASD subjects only to wins but not to losses, and further highlighted a differentiation in the repetitive behaviours that was sensitive to switch of frames. Repeated measures ANOVA of reaction time also identified a significant group x ‘switch of frames’ interaction, which showed a significantly higher ‘cost’ of reaction time whilst context switched. This prolonged time from evaluating potential wins to potential losses implied that the response speed amongst ASD subjects was more vulnerable to contextual change. Methodologically, these adaptive changes on a temporal scale and the effect of switching frames validated the block design and the ‘win condition comes first’ manipulation. In the gambling test, robust effects between conditions were found in risk-taking behaviours. It is reasonable to suspect that the identified vulnerability to contextual change would be fundamentally different between a switch from win to loss, and a switch from loss to win. We admit that the win condition always came before the loss condition design is not the ideal experimental design and has its own artefact. Nevertheless, in order to examine sensitivity to switch of frame s amongst a pathological group of subjects diagnosed with rigid interest and repetitive mannerism, the current experimental design provides a fair comparison to investigate the unique risk-taking strategy of ASD subjects that requires the less turbulence as possible.

Chapter 4. PFC battery - the referential judgment test

4.1 Measurements for preference consistency on social vs. non-social judgements

In previous psychometric paradigms involved measuring decision-making between multiple options, subjects were required to choose the preferred option based on their personal preference. During the decisional process, it was suggested that choosing one option over others signified a respective rank on one's internal scale (Lebreton, Jorge, Michel, Thirion, & Pessiglione, 2009). Importantly, this comparative process involved choosing one over another could be vulnerable to context, e.g., the framing effect demonstrated a tendency for people to take more risky actions to avoid potential losses than to pursue potential gains. An important modulating factor of this context-sensitive effect was the uncertainty of the outcome, where the outcomes of the possible gains or losses were sometimes unpredictable. Nevertheless, the problems we encountered in everyday life were not always accompanied with uncertainty, and the decisions could be made without facing ambiguous context. For example, Fellows & Farah (2007) used a preference judgment paradigm to examine the functional role of the PFC region played in decision-making. The basic procedure of this preference judgment test was that subjects were required to choose between paired stimuli in three different categories (food, famous people and colour swatches). Subjects were instructed to choose the item they preferred without reference to their previous choices, but were not specifically reminded to be internally consistent on responding. The dependent variable of the preference judgment test was the number of erratic choices deviated from the overall pattern of preferential choices based on one's own internal metric in each category. In order to make fewer erratic choices, subjects needed to construct their own preferential hierarchy and responded consistently. The result showed that patients with lesions in the ventromedial PFC region responded more inconsistently than the controls by making more choices that are erratic. This impairment indicated that the PFC region was involved with decision-making processes under situations without uncertainty or any trial-by-trial learning, and actions could be made based on internal metric without considering external effects. This consistent responding ability relied more on self-awareness, or self-referential processing, which was evident to associate with the ventromedial PFC region (Mitchell et al., 2005). This raised the importance of the functional role of 'self' played in decision-making. Despite the preference judgment paradigm (Fellows and Farah, 2007; Fellows, 2011; Henri-Bhargava, Simioni and Fellows, 2012) provided evidence on the linkage between consistent decision-making and the ventromedial PFC region, the potential role of self-referential processing played was not discussed.

In the area of investigating the concept of 'self' in human cognition, it was identified that words were remembered better when encoded with self-referential processing, and this enhanced memory effect was referred as the self-reference effect (SRE). For example, Rogers, Kuiper, & Kirker (1977) investigated the effect of self-reference during encoding could affect later recall on the rate words in a memory paradigm, and found that the adjectives rated under the self-reference condition, compared other conditions, and were recalled the best. The basic structure of the experiments measuring SRE effect involved first memorising some words in an encoding phase, and subjects were required to make judgments on the words based on their personal relevance, e.g., after presenting the words, subjects responded to the question, "Does this describe you?" In the following testing phase, a new set of words mixing with words from the encoding phase were presented to subjects. This enhanced memory performance suggested that information relevant to one's own is processed and/or stored in a more elaborate form than other types of information, which subsequently led to better memory performance. Benoit, Gilbert, Volle, & Burgess (2010) also used a recognition memory paradigm to measure self-referential processing, and further examined if this cognitive process supported thinking about other people. In the study phase, personality trait words were presented and subjects needed to indicate the degree of the traits were descriptive of themselves in the 'self' condition, judge where their best friend would be characterised by those traits in the 'other' condition, and count the number of syllables of the trait words in the 'control' condition. Both old and new words were presented in the subsequent testing phase, and half of the trait words were encountered in the corresponding study condition (old/same), and the other half were either shown in the other two conditions (old/different) or not presented (new). The behavioural result demonstrated a more accurate performance in the 'self' than other two conditions, which was consistent with the enhanced memory performance for information involved self-referential processing. However, these memory effects, including the SRE effect, were observed using memory paradigm, which inevitably would involve possible confound from mnemonic capability between individuals. More importantly, personally relevant information would be inherently encoded at a deeper level than other information, as the original depth-of-processing model proposed by Craik and Tulving (1975). It is therefore necessary to examine the advantage of self-reference processing, if true, using other experimentation that differentiated self-related from self-unrelated processing more directly.

In the current referential judgment test, we combined the rationale behind the preference judgment test and the insight suggested by the SRE effect, and developed a novel experimentation aimed at measuring the ability to construct one's own internal hierarchy relying on referential judgments instead of preference (c.f., the preference judgment paradigm). Based on the finding from Benoit et al. (2010), it revealed a better recognition for trait words encoded as similar to one's own than trait words encoded as similar to the best friend's. A key differentiation between these two conditions was the involvement of processing self-related information (personality of self) and of processing self-unrelated information (personality of other's). As a result, the experimental stimuli we used were in two different dimensions, a self-related construct and a self-unrelated construct. The self-related construct was one's own personality, which involved referencing to 'self' information. On the other hand, the self-unrelated construct was the weight of bottle water, and referencing to this information presumably rely relatively lower amount of self-information. During the test, Instead of asking subjects to choose the preferred item between two options as in the preference judgment paradigm, we asked subjects to choose the person with the personality most like theirs in the personality condition, and to choose the object with the weight most like bottle water in the weight condition. For the variables measuring the degree of self-related vs. self-unrelated processing, we used a 'consistency score' to demonstrate the response consistency during referential judgment. The rationale behind this consistency score was that the better understanding of self, the higher degree of consistency, or better-organised internal hierarchy would be established. More detailed information of this consistency score would be described in the Methodology section. In the referential judgment test, subjects were required to construct their own hierarchical metric according to a self-related reference and a self-unrelated reference. Based on previous studies suggesting deeper processing of self-related information (Craik and Tulving, 1975), as well as the enhanced memory performance related to self-processing in SRE experiments, we hypothesised that the consistency score we calculated, which measured the ability to establish internal hierarchy, would be higher when referencing to one's own personality than referencing to the weight of bottle water. In Benoit et al (2010), analysis on response times revealed that subjects responded faster in the 'self' than in other two conditions. As a result, we hypothesised that the reaction time would be faster in the personality condition than in the weight condition. Lastly, in order to compare the established internal hierarchy between relying on self-related vs. self-unrelated information, we also examined the distribution of the top-ranked item between individuals.

4.2 Methods of the referential judgment test

<u>Materials and Design</u>

There were two conditions in this referential judgment test: a personality condition and a weight. In the personality condition, pairs of human faces with neutral expression were presented side-by-side on the screen. The 12 colourful faces were extracted from the Centre for Vital Longevity Face Database (Minear and Park, 2004) including males and females, age ranging from 19-29 and differing in four ethnicities (East Asian, Indian, African-American, and Caucasian). In the weight condition, pairs of daily objects were presented side-by-side on the screen. The 12 colourful objects were extracted from shopping websites on the internet including items weighing from 0.1 kilograms to 5 kilograms. The face stimuli in the personality condition were presented 8 x 10 cm in size and the objects in the weight condition were presented 8 x 8 cm in size. All possible 66 pairs of stimuli in each condition were presented in the same order across all subjects (see Figure 4.1 for all stimuli).

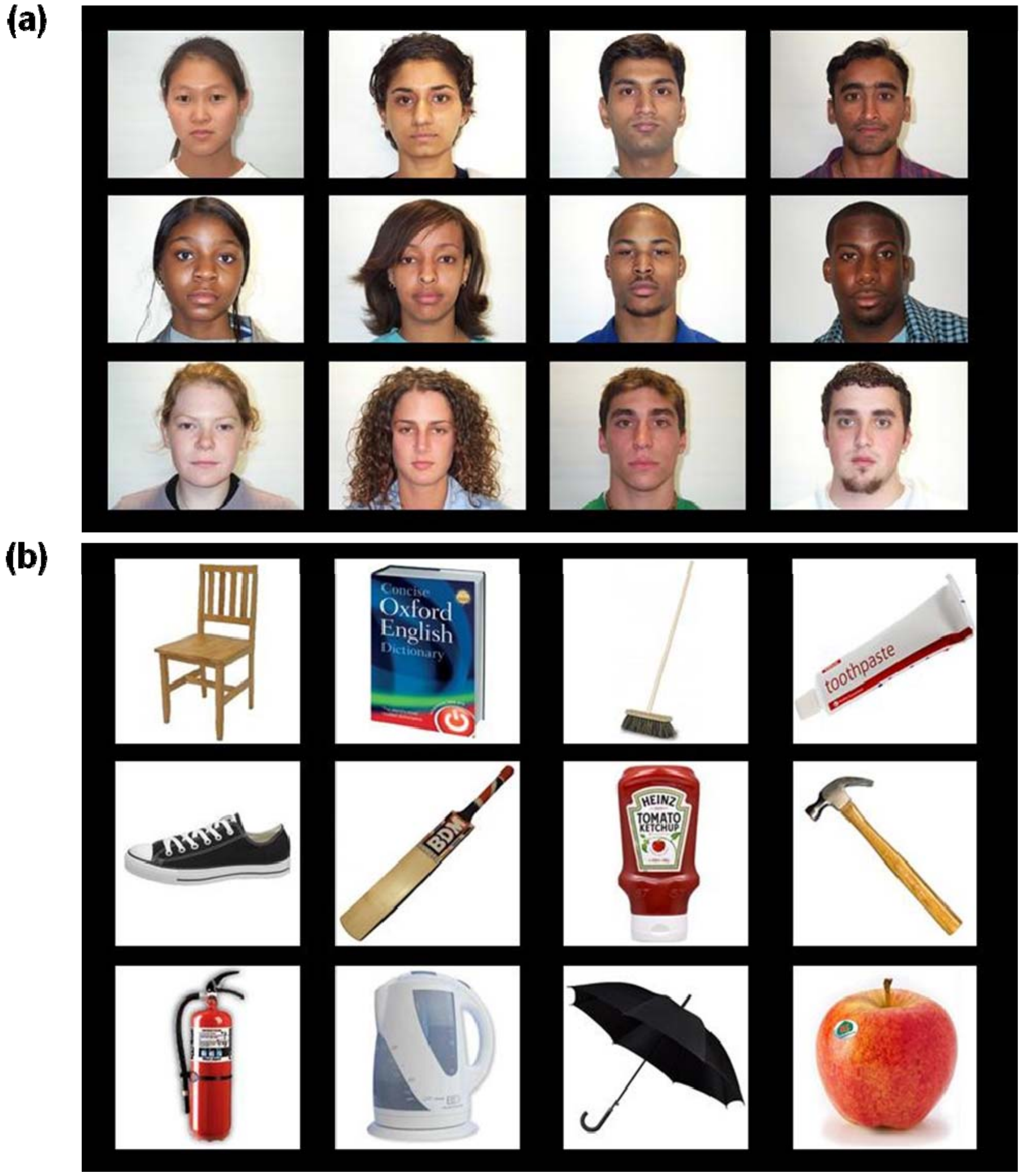


Figure 4.1. The experimental stimuli for the referential judgment test. Panel (a): male and female neutral face stimuli varying in ethnicities. Panel (b): common daily objects varying in weight from 0.1 kilograms to 5 kilograms.

Procedure

Before the beginning of the referential judgment test, an instruction with two practice trials of each condition was given. In the personality condition, 66 pairs of colourful neutral faces were presented side-by-side on the screen (see Figure 4.2). Subjects were told to choose the face with the most similar personality as theirs by pressing the corresponding left or right arrow keys. The instruction emphasised that the decisions could be based on any characteristics of the faces presented including gender, ethnicities, or any other facial attributes. In each trial, a cue saying ‘my personality is more like…’ was presented on the screen for 500 milliseconds, and a pair of faces was presented on the screen until a response was made. After a response was registered, the option selected was highlighted with a green outline for 500 milliseconds, and the next trial was presented after another 500 milliseconds of blank screen. In the weight condition, 66 pairs of colourful objects were presented side-by-side on the screen. Subjects were told to choose the object with the most similar weight to a bottle of water by pressing the corresponding left or right arrow keys. In each trial, a cue saying ‘the weight of a bottle of water is more like…’ was presented on the screen for 500 milliseconds, and a pair of objects was presented on the screen until a response was made. The selected option would be highlighted with a green outline for 500 milliseconds, and the next trial was presented after a 500 milliseconds of blank screen. The referential judgment test took each subject approximately 15 minutes to finish. All subjects were asked to administer the personality condition first, and then the weight condition.

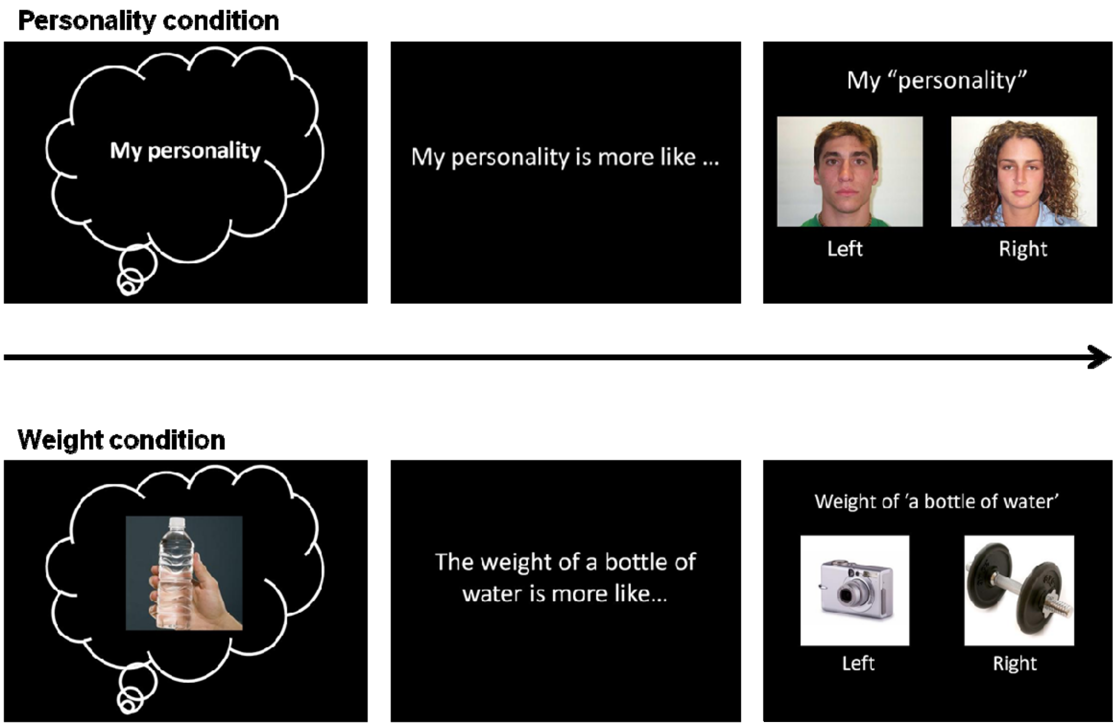


Figure 4.2. The experimental procedure for the referential judgment test. In the personality condition, subjects were required to make referential decisions using their own personality as the reference. In the weight condition, subjects were required to make referential decisions using the weight of bottle water as the reference.

Measurements

To measure individuals' response patterns in referential judgment, a Repertory Grid (Kelley, 1955) approach was used to calculate a score demonstrating the 'consistency' of decision-making in each condition. The rationale of this Repertory Gird analysis was to examine the ability to build up a perfect hierarchy of referential judgments amongst all the possible options. For example, imagine that there were three options, A, B, and C, and three options were compared with each other. If someone chose A over B and B over C, then a perfect hierarchy would expect a response choosing A over C in order to be internally consistent. This outcome would lead to a series of responses where A was chosen two times, B was chosen one time, and C was chosen zero time. The Repertory Grid method would give: A=2, B=1, C=0, showing a perfect range with no ties. As a result, this would yield a range of 3, or in in terms of the referential judgment test here, a consistency score of 3. By contrast, a response choosing C over A would be considered as an erratic choice or a violation of the perfect hierarchy and the Repertory Grid method would give this: A=1, B=1, C=1, given that A, B and C were all chosen one time. This leads to a range of 1 with three ties, or a consistency score of 1. In the referential judgment test designed here, the consistency score ranged from a perfect score of 12 to the lowest possible score of 2. A higher consistency score demonstrated a more consistent set of referential judgments that were made presumably based on one's own internal metric. In addition to the consistency score, the reaction times to each response were also recorded.

The consistency score thus represented the internal mental scale derived from each subject. The most frequently chosen option would be considered the referential 'preference' in each condition. In the personality condition, the most preferred item can be the most similar personality as the subject with the highest relevance. It is possible that, according to the SRE effect, subjects would respond faster to the most preferred faces when self-referential processing was involved (see Benoit, Gilbert, Volle, and Burgess, 2010, for similar acceleration when comparing self-trait judgments with control condition). In order to examine if any particular response pattern was applied to the most preference item in each condition, we further extracted individual's reaction times to the most preferred item on a post-hoc basis.

4.3 Behavioural result of the TD group

The ranking scheme between conditions

The top-ranked item in each condition of each subject was first identified. In the personality condition, the item got selected as the top-ranked varied between individuals, i.e., each of the twelve possible options was ranked as the top item at least once, and the number of TD subject choosing each of the top-ranked items ranged from 2% to 17% of the 107 TD subjects (see Table 4.1, and Figure 4.3 for illustration). In the weight condition, the item was selected as the top-ranked was clustered at one particular item, where 55% of the subjects considered a ‘ketchup’ bottle have the most similar weight as bottle water. Nine of the twelve items were selected having the most similar weight as the reference by less than 5% of the subjects, and two items were never ranked as the top across 107 TD subjects.

Table 4.1. The frequency and proportion to the top-ranked faces in the personality condition, and the top-ranked object in the weight condition between each TD subjects. For subjects who had ties, e.g., two ties, in their ranking scheme, the frequency top-ranked items were counted as multiple times, e.g., twice.

Personality condition			Weight condition		
Face no.	Frequency	Proportion	Object no.	Frequency	Proportion
1	11	0.08	1	0	0.00
2	12	0.09	2	2	0.02
3	11	0.08	3	1	0.01
4	10	0.07	4	3	0.02
5	23	0.17	5	1	0.01
6	19	0.14	6	1	0.01
7	9	0.07	7	71	0.55
8	11	0.08	8	6	0.05
9	7	0.05	9	21	0.16
10	10	0.07	10	7	0.05
11	12	0.09	11	2	0.02
12	3	0.02	12	13	0.10

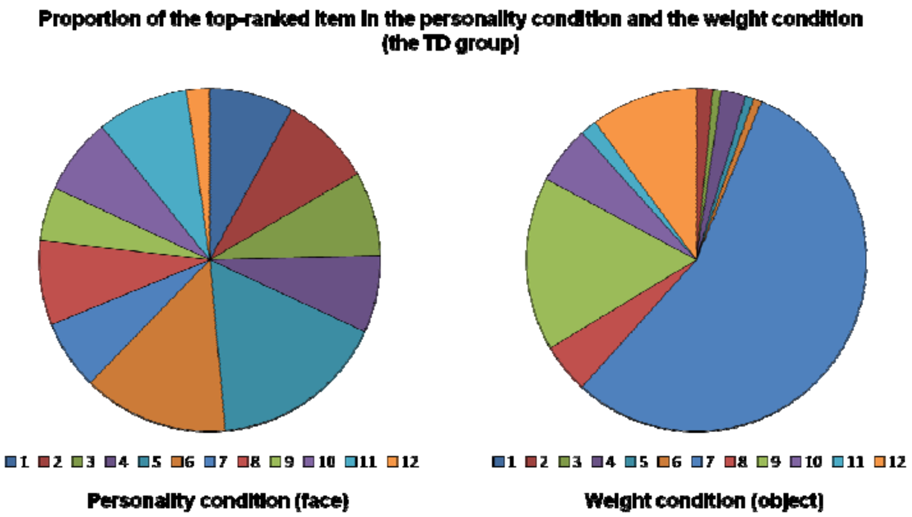


Figure 4.3. The ranking scheme of the top-ranked items in the referential judgment test.

Behavioural results between conditions

The behavioural results of the TD were summarised in Table 4.2. Repeated measures ANOVA revealed a significant effect of condition ($F(1,106)=11.954$, $p=0.001$), where consistency score was significantly higher in the weight condition than in the personality condition. Repeated measures ANOVA on overall reaction time also demonstrated a significant effect of condition ($F(1,106)=18.470$, $p<0.001$), which showed that the response time was significantly faster in the weight condition than in the personality condition.

Table 4.2 The mean and standard deviations of consistency score and the overall reaction time (msec.) between conditions in the referential judgment test of the TD group.

	mean	SD
Personality condition		
Consistency score	8.46	1.38
Reaction time (msec.)	1946.5	1080.7
Weight condition		
Consistency score	9.01	1.43
Reaction time (msec.)	1560.6	553.0

Correlation analysis

Due to all the variables deviated from normal distribution (p value below 0.05 in test of normality), Spearman's rank-order correlation analysis was conducted to examine the relationship between experimental variables in the referential judgment test. In the first approach, we focused on the within-variable effect, where the relationships on consistency score between conditions (personality and weight) and overall reaction time between conditions were examined. In the second approach, we analysed the between-variable effect, where the relationships between the two experimental conditions using consistency score and overall reaction time were examined separately. In the first approach, Spearman rank-order correlation analysis showed that both consistency score (r_s (107)=0.263, p=0.006), as well as overall reaction time (r_s (107)=0.669, p<0.001) were positively correlated between the two conditions. Correlation analysis on the between-variable effect found the relationship between consistency score and overall reaction time was not significant in the personality condition (r_s (107)=-0.011, p=0.912), but positively significant in the weight condition (r_s (107)=0.257, p=0.008).

4.4 Discussion of the behavioural result in the TD group

The referential judgment test used a Repertory Grid approach to measure the response consistency on decision-making processing based on self-related and self-unrelated references separately. The investigation of the item ranking scale between conditions across individuals showed that the top-ranked item was more variable between subjects when referencing to one's own personality, but the top-ranked item was more agreeable between subjects when referencing to the weight of bottle water. This fundamental difference on the ranking scheme amongst options between TD individuals demonstrated the impact of self-referential processing, which was demonstrated by the higher variability when decision process relied on self-related information. On the other hand, making referential judgments to the weight of bottle water, a less abstract reference than self, involved lesser degree of self-evaluation, and thus led to higher agreement between individuals. The results on the difference between ranking schemes in the personality and the weight condition supported the distinct underlying process of the referential judgment under self-related and self-unrelated situations

Analysis on the ranking scheme provided measurements of referential decision across all of the options, yet analysis on consistency score focused on the degree of response pattern fixated on the chosen option. Repeated measures ANOVA found that consistency score was significantly higher and overall reaction time was significantly faster in the weight condition than in the personality condition. This contradicted with our original hypothesis that referential judgments, which supposed to involve with self-evaluation, would lead to enhanced performance as demonstrated by the SRE effect and Benoit et al. (2010). This discrepancy might be due to the nature of the referential decision between conditions, as revealed by the analysis on the ranking scheme. In the weight condition, the reference was the weight of a tangible object, and the referential judgment involved lesser degree of self-evaluation. Subsequently, this made the construct of the weight less abstract, where subjects might find it easier to build a consistent hierarchical metric. This raised an interesting issue regarding the enhanced effect on self-referential processing, which might not contribute to performance measured by item-based analysis like the Repertory Grid approach in the current test. For example, in order to get higher consistency score, subjects were required to make decisions based on a consistent rank. If a ranking scheme is not only more agreeable across subjects, but also easier to build based on a tangible construct, it is not surprised that the internal hierarchy could be built more easily, and subsequently led to higher consistency score and faster reaction time.

We further analysed the relationship between the variables measured in the referential judgment test. Spearman order-rank correlation analysis showed that the consistency score was positively correlated with each other in the two conditions. This significant relationship posited a possible shared underlying process to establish a consistent internal metric based on self-related and self-unrelated constructs. This positive correlation also provided an insight on the null effect of self-referential effect, where the scoring mechanism of the consistency score might have a profound effect on the cardinal feature we tried to compare against each other. In other words, the Repertory Grid approach we implemented might capture some other cognitive components that associated with referential judgments, but eliminated the effect of 'self' by the scoring scheme. Nevertheless, correlation analysis on the between-variable effect did not find a significant relationship between consistency score and overall reaction time in the personality condition, but significant in the weight condition. This distinct correlation between conditions suggested some fundamental difference upon the ‘speed-accuracy’ interaction, where subject made slower decisions did not necessarily associated with better consistent referential judgments relied on self-related construct. On the other hand, the positive significant relationship between consistency score and overall reaction time in the weight condition revealed that referential processing based on self-unrelated construct seemed to be an intuitive act instead of confined by the classic ‘speed-accuracy trade-off’ observed in psychometrical experiments. More investigations were required to discover the underlying process that resulted in the mixed effects here. Together the results showed that self-referential processing, or decision-making processes based on self-related information might not always associated with advantageous effect.

4.5 Neuroimaging findings of preference consistency on social vs. non-social judgements

In typically-developing brain, abundant evidence has established the linkage between processing self-related information and the ventromedial part of the PFC region. For example, the ventromedial PFC activations were observed in tests involved trait judgment involving self-referential processing (Mitchell, Banaji, & Macrae, 2005; Mitchell, Macrae, & Banaji, 2006), requiring subjects to report their own personalities or preferences (Schmitz et al., 2004; Benoit et al., 2010), reflecting their own affective states (Gusnard, Akbudak, Shulman, & Raichle, 2001), and accompanied with enhanced memory performances for self-related information (Macrae, Moran, Heatherton, Banfield, & Kelley, 2004). Some researchers suggested that this self-referential processing played an essential role in social cognition, where people implemented their own experience to make inferences on the mental states of others (Frith & Frith, 1999; 2001; Gallagher & Frith, 2003; Mitchell et al., 2005), and was referred as the simulation theory. For example, Mitchell et al. (2005) used fMRI to investigate the linkage between processing information about self and the medial PFC region. Functional results revealed that ventromedial PFC activity was shown to correlate with perceived self/other similarity only for mentalizing trials. This confirmed the linkage between self-reflection and making inferences of others that were similar to self. A possible explanation of this linkage between self and others was based on the unique anatomical connections between the medial PFC region and other cortical regions (Passingham, Bengtsson, Lau, 2009). In previous self-judgment tests, subjects were required to reflect on, or introspect about their own inner mental states, personalities or preferences (Johnson, Baxter, Wilder, Pipe, Heiserman, & Prigatano, 2002; Zysset, Huber, Ferstl, & von Cramon, 2002). Neural activity in the medial PFC region was shown to selectively engaged in self-referential judgments about trait adjectives (Kelley, Macrae,Wyland, Caglar, Inati, & Heatheron, 2002), correlated with subjects' subsequent ratings of self/other similarity during mentalizing trials (Mitchell et al., 2005), differentiated self from others for personality traits, mental states and physical attributes (Jenkins and Mitchell, 2011), and further suggested to involve with self-representation of both personality traits and social identities (Sul, Choi, & Kang, 2011).

In the current referential judgment test, as described in chapter 4-1, was developed by following the rationale behind the preference judgment paradigm (Fellows and Farah, 2007). However, participants were required to make referential decisions instead of making decisions based on their preference. The referential judgment test contained a personality condition that involved self-referential processing, and a weight condition that did not require, or in a lesser degree of self-referential processing. Subjects were required to make referential decisions to all the competing face/object pairs as test progressed based on the internal construct of their own, and eventually established a hierarchy using a ranking scheme to identify the most similar face/object. In a similar paradigm, in order to investigate the neural processes with and without self-referential processing, Johnson et al. (2006) compared the neural activity in the 'internal subjective decision' condition requiring overt self-referential processing (e.g., subjective decision about colours) with the 'external subjective decision' condition that did not require self-referential processing (e.g., colour similarity). The result found greater medial PFC activity in the condition with self-referential component, and further suggested that the medial PFC specifically involved with processing self-related thoughts, rather than to any subjective judgments. In the referential judgment test, we used a 'consistency' score based on the Repertory Grid approach to measure the degree of making consistent referential judgment relied on a perfect hierarchy. To obtain higher consistency score, subjects needed to make trial-by-trial adjustments to override the existing internal metric in order to update the hierarchy after each referential decision. For example, if on three consecutive trials, A vs. B, A vs. C, A vs. D, and a subject responded A over B, A over C, but when it comes to A vs. D, the subject chose for D over A. In this case, option A was no longer at the highest rank and one ought to override the old internal metric and establish a new hierarchy as test progressed. The adaptive ability to override a predominant behavioural pattern in accordance with contextual changes is essential for survival. The underlying process of this 'switch' from a routine behaviour to a new one according to changes of environment or rules was referred as cognitive flexibility. Previous fMRI studies using psychological paradigms like the Stroop test (Stroop, 1935) or the Wisconsin

Card Sorting test (Heaton, 1981) revealed that the PFC region was essential for tests required cognitive flexibility (Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Rougier et al., 2005). Specifically, a classic psychometric paradigm measuring cognitive flexibility, the reversal-learning paradigm, required subjects to override a previously dominant response-feedback association, and switched to another competing alternative due to the change of feedback contingencies. Previous lesion and fMRI studies have established robust association between the score of reversal learning and the lateral OFC region (Greening et al., 2011; Hampshire et al., 2010; Hampshire et al., 2012). In the referential judgment test, subjects were required to establish their own internal hierarchy either relying on self-related personality in the personality condition or self-unrelated weight of bottle water in the weight condition. The higher the consistency score signified a higher capability to override the existed metric and eventually identified the top-ranked face based on self-referential processing. On the other hand, in the weight condition, the higher the consistency score demonstrated a higher capability to override the out-of-date hierarchy and choose the top-ranked object consistently, and the referential judgements here did not require self-referential processing, compared with the personality condition. As a result, we hypothesised that the consistency score in the personality condition would correlate with GM volume in the medial PFC region due to the involvement of self-referential processes. In contrast, in the weight condition, we hypothesised that the consistency score would correlate with GM volume in the lateral OFC region, given that no self-referential decisions were involved and the underlying process was similar to the core feature of cognitive flexibility in reversal learning paradigm.

4.6 Behavioural and VBM result of the TD sub-group

Behavioural investigation into the referential judgment test

The behavioural results of the TD sub-group were summarised in Table 4.3. Repeated measures ANOVA revealed a significant effect of condition ($F(1,61)=8.626$, $p=0.005$), where consistency score was significantly higher in the weight condition than in the personality condition. Repeated measures ANOVA on overall reaction time also demonstrated a significant effect of condition ($F(1,61)=7.336$, $p=0.009$), which showed that the response time was significantly faster in the weight condition than in the personality condition.

Table 4.3. The mean and standard deviations of consistency score and the overall reaction time (msec.) between conditions in the referential judgment test of the TD sub-group (n=62).

	mean	SD
Personality condition		
Consistency score	8.48	1.36
Reaction time (msec.)	2014.0	1247.5
Weight condition		
Consistency score	9.10	1.34
Reaction time (msec.)	1629.3	604.7

Spearman rank-order correlation analysis on the within-variable effect did not find a significant relationship between consistency score in the two conditions (r_s (62)=0.227, p=0.077), but a significant correlation was identified between overall reaction time in the two conditions (r_s (62)=-0.639, p<0.001). Between-variable effect revealed a positive significant correlation between consistency score and overall reaction time only in the weight condition (r_s (62)=0.360, p=0.004), but not in the personality condition (r_s (62)=-0.037, p=0.773).

VBM investigation into the referential judgment test

The VBM results were summarised in Table 4.4. VBM regression analysis found no significant correlation between consistency score in the personality condition and the GM volume in the medial PFC region. Instead, a marginal positive correlation was found between consistency score in the personality condition and a GM cluster located in the right lateral OFC region at [47, 30, -5] (SVC: AAL_Frontal_Inferior_Orbital_Right, p=0.051). A negative correlation was also found between consistency score in the personality condition and the GM volume in the left lateral OFC region at [-30, 21, -18] (SVC: AAL_Frontal_Inferior_Orbital_Left, p=0.015) (see Figure 4.4(a)). In the weight condition, a positive significant correlation was identified between consistency score and the GM volume in the right lateral OFC region at [56, 21, -8] (SVC: AAL_Frontal_Inferior_Orbital_Right, p=0.011) (see Figure.4.4(b)).

Table 4.4. The VBM result of the referential judgment test. The GM clusters in the PFC region showing significant correlations with consistency score in the referential judgment test between conditions (p<0.001, uncorrected for whole brain analysis, and p<0.05, FWE-corrected for SVC using different ROIs derived from the AAL atlas). Brodmann areas are approximate, (+) indicatespositive relationship and (-) indicates negative relationship.

	p<0.001, uncorrected				Small Volume Correction (FWE<0.05)			
	Whole brain analysis				AAL_Inferior_Orbital		AAL_Superior_Medial	
	k	t	MNI	Label	p	MNI	p	MNI
Personality condition								
Score (+)	24	3.55	[47, 30, -5]	BA47	0.051	[47, 30, -5]		
Score (-)	212	4.00	[-30, 21, -18]	BA47	0.015	[-30, 21, -18]		
	39	3.84	[23. 23. 54]					
	33	3.76	[48, 18, 30]					
Weight condition								
Score (+)	60	4.13	[56, 21, -8]	BA47	0.011	[56, 21, -8]		
Score (-)	192	4.09	[-48, 26, 16]					

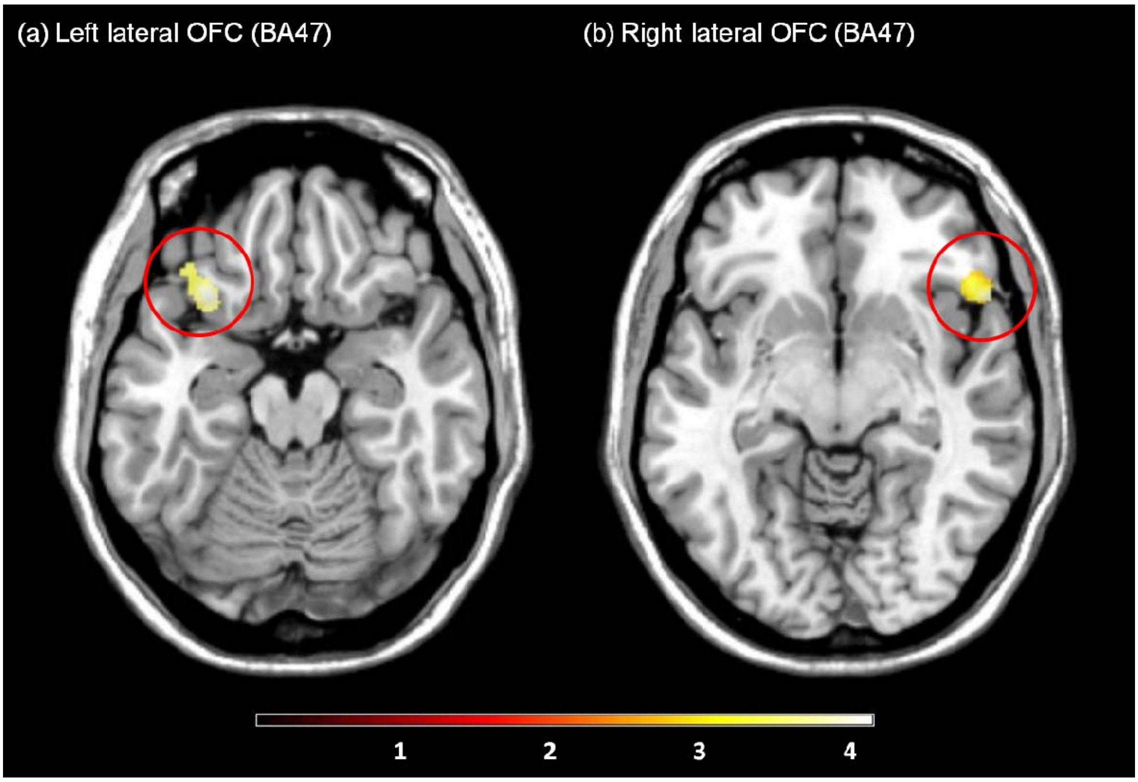


Figure 4.4. The GM volume that significantly correlated with the variables in the referential judgment test. (a) Consistency score in the personality was negatively correlated with a GM cluster located in the lateral OFC region. (b) Consistency score in the weight condition was positively correlated with a GM cluster located in the lateral OFC region.

4.7 Discussion of the VBM result in the TD sub-group

The behavioural part of the result on the TD sub-group demonstrated the same findings as the baseline performance established by the TD group. Repeated measures ANOVA found that consistency score was significantly higher and overall reaction time was significantly faster in the weight condition than in the personality condition. Correlation analysis on the TD sub-group did not find a significant relationship between consistency score between the two conditions, but replicated other findings identified in TD group showing significant relationship on overall reaction time between the two conditions. Importantly, the correlation between consistency and overall reaction time was only significant in the weight but not in the personality condition, which was also consistent with the observed distinction observed in the TD group. The only discrepancy was the null relationship between consistency in the personality and the weight conditions. We suspected that it was due to the relatively smaller sample size, given that the correlation coefficients were similar between the analysis using the TD group (r_s (107)=0.263, p=0.006) and the TD sub-group (r_s (62)=0.227, p=0.077). Other statistical analytic method, e.g., principal component analysis, could provide further examination of the relationship between consistency score under situations relying self-related vs. self-unrelated construct, which would be described in the later chapter.

For the VBM results, regression analysis did not find a significant correlation between the consistency score in the personality condition and any GM volume in the medial PFC region. This indicated that the ability to make consistent referential decisions based on self-referential processing did not necessarily associate with the regional volume in the medial PFC region. Nevertheless, it should be emphasised that this lack of function-structure relationship did not fundamentally rule out the functional role of the medial PFC played in self-referential processing. Instead, a negative correlation was found between consistency score in the personality condition and the left lateral OFC region. As suggested by reverse-learning paradigm, the lateral OFC region was evident to involve with cognitive flexibility. A possible explanation for this relationship between left BA47 region and consistent decision in the personality condition might be related to processing of face identities.

For example, Labar, Crupain, Voyvodic, & McCarthy (2003) examined brain activations associated with dynamic changes in facial identity or emotional expressions. In the facial identity condition, facial stimuli depicting one person were morphed that it gradually changes to another. The result showed that a dorsal fronto-cingulo-parietal circuit, including a GM cluster at [-30, 19, -8], was involved with such changes. In the current study, pairwise facial stimuli were presented sequentially during the personality condition. When viewing different faces sequentially, it is possible that a mental process similar to the identity condition in Labar et al. (2003) would be engaged. A critical aspect in the personality condition was the ability to identify physical features in different faces upon making referential decisions using self-related construct. It is therefore possible that this observed function-structure relationship in the personality condition reflect the capability to identify important features during referential processing.

In the weight condition, a positive significant relationship was found between consistency score and the GM volume in the right lateral OFC region. This was consistent with our hypothesis that mental ability involved overriding predominant internal metric based on self-unrelated construct was associated with the GM volume in the lateral OFC region, as identified in the reversal-learning paradigm. Nevertheless, a critical difference between the referential judgment test and the reversal-learning paradigm was the lack of feedback after decisions. Hampshire and colleague (2012) used a reversal-learning paradigm to examine the contributions of different PFC sub-regions during various time points including processing negative feedback, initiation of new search, reversal, and switching from one object to another. The results showed that both lateral OFC and lateral PFC responded at the point of reversal. Specifically, the lateral OFC region was differentially activated during the point of ‘switch’ following contingency reversal, whereas the lateral PFC region was activated during all switching points. This indicated that the functional role of the lateral OFC in reversal learning was more specific to change of contingency between stimulus-response mappings. As a result, it is possible that the BA47 – weight consistency score implied that the ‘consistency’ score we used actually measured the ability relating to switch, or to override existed contingency of the internal hierarchy, to be precise. In our original speculation, the higher the consistency score supposed to reflect higher degree of consistent decision upon higher-ranked item. It might sound paradoxical at first, but a higher consistency score could also reflect a higher capability to override the existed contingency based on old ranking scheme and kept updating while more preferable options were introduced as the test progressed. Together the VBM results suggest a stimulus-specific relationship between consistency score in the personality condition and the left lateral OFC region, as well as a potential linkage between consistency score in the weight condition and cognitive flexibility.,

4.8 Atypical behaviours relating to preference consistency on social vs. non-social judgements in ASD subjects

A ‘self’ related deficit has been long proposed in ASD, even before it was clinically diagnosed. The word ‘autism’ was derived from the Greek word ‘autos’ and translated as ‘self’. Early stage studies by Kanner and Asperger had coincidentally described fundamental features as ‘extreme autistic aloneness’, and ‘autistic psychopathy’ respectively. Early observations of ASD symptoms reported extreme egocentrism, and referred to them as locked in a world of their own, which seemed unreachable by other people. Evidentially, individuals with ASD were found to have impairments on self-referential processing, which was demonstrated by the observed deficit on self-reference effect (SRE), where ASDs failed to show enhanced memory performance on self-referentially encoded information via an elaborational or organisational mechanism in autobiographical memory (Rogers, Kupier, & Kirker, 1977; Klein & Loftus, 1988). For example, Lombardo, Barnes, Wheelwright, and Baron-Cohen (2007) measured the SRE effect in adults with ASD in a paradigm asking subjects to judge how descriptive personality traits words were related to 'Self', 'Friend', 'Harry Potter', and syllable counts. The SRE effect was found to attenuate in ASD subjects between the scores of 'Self' and 'Harry Potter' conditions, which showed a reduced recognition memory effect on words processed in relation to self. Critically, comparison of the SRE effect between groups in each condition revealed significantly worse memory performance for traits of 'Self' and 'Friend', but not of 'Harry Potter'. This indicated a differentiation of social processing in self-referential deficits, where reduced performances were observed in close/similar others ('Friend'), but not in non-close/dissimilar others.

The observed egocentrism and self-referential deficits in ASD were previously characterised as the 'absent-self' hypothesis (Frith and Happe, 1999; Frith, 2003; Happe, 2003; Baron-Cohen, 2005). The idea of this hypothesis was based on an abnormal top-down control mechanism that failed to regulate bottom-up information in the autism brain. To support this hypothesis, previous neuroimaging studies demonstrated atypical modulations in the frontal regions (Ring et al., 1999; Lee et al., 2007; Manjaly et al. 2007), and enhanced short-range but diminished long-range connectivity associated with the frontal region (Just, Cherkassky, Keller, & Minshew, 2004; Courchesne and Pierce, 2005). Lombardo et al. (2010) recruited male ASD adults with matched male controls and asked them to make mentalizing judgments or physical judgments about themselves or the British Queen. The result found that neural activity in control subjects preferentially recruited the ventromedial PFC region in the self vs. other contrast, whereas ASD subjects revealed equal ventromedial PFC activation. Furthermore, ASD subjects also demonstrated atypical neural network associated with the PFC region, where neural response for self-referential processing was observed by showing reduced functional connectivity between the ventromedial PFC and areas associated lower-level processing including premotor and somatosensory cortex. Together these results revealed an atypical brain mechanism relating to self-referential processing observed in the ventromedial PFC region, and was consistent with the ‘absent-self’ hypothesis in ASD individuals.

In the referential judgment test, we followed the rationale of the preference judgment paradigm (Fellows and Farah, 2007), and asked subjects to make referential decisions based on self-related construct (personality) in the personality condition and on self-unrelated construct (weight) in the weight condition. In the personality condition, subjects engaged in trial-by-trial referential judgments between two competing options, and the decisions could be made based on any physical characteristics of the presented faces. The ‘anchored’ reference was one’s own personality, which involved with processes centred on self-related representation. On contrary, in the weight condition, subjects also engaged in trial-by-trial referential judgments between two options, but the ‘anchored’ reference was the weight of bottle water, which involved with processes without self-referential component. Previous studies suggested that medial PFC differentially activated for subjective decision-making with and without self-referential processing (Johnson et al., 2006), and ASD subjects had specific impairments on elaborating or organising self-related information (Lombardo et al., 2007), as well as atypical neural mechanism in the ventromedial PFC region (Lombardo et al., 2010). However, the

VBM results demonstrated by the TD sub-group failed to identify any GM volume in the medial PFC region was correlated with consistency score in the personality condition. Instead, consistency score in both conditions (marginal significant in the personality condition) reflected a positive relationship with the GM volume in the right lateral OFC, or ventrolateral PFC region. As discussed earlier, this raised a possibility that the response consistency we calculated in the referential judgment test measured other cognitive processes that were not expected, e.g., cognitive flexibility. Incidentally, it was shown that ASD subjects had deficits on cognitive flexibility using a range of tests (see Hill, 2004; Geurts, Corbett, & Solomon, 2009 for review). For example, the Intradimensional-Extradimensional shift (ID/ED shift) test from the Cambridge Neuropsychological Test Automated Battery (CANTAB) measured the cognitive control process that required shifts within and between dimensions. In the ID/ED shift test, the first five levels involved learning to respond selectively to specific targets, and the next four levels (6-9) provided measurements on the number of trials to achieve criterion and the number of errors committed for rule violations. In level 6 and 7, where ID-shift and ID reversal were introduced, subjects needed to ignore previous rules within dimension. In level 8 and 9, where ED-shift and ED reversal were introduced, subjects needed to respond to previously ignored rule between dimensions. Errors on rule acquisition and inhibition during later stages illustrated cognitive inflexibility as a function of increase in rule complexity. Ozonoff et al. (2004) implemented the ID/ED shift test on ASD subjects and found more errors were made in stage 8 and 9, compared to control participants. A similar psychological paradigm measured cognitive flexibility that highlighted the role of reversal was the reversal-learning paradigm. The critical aspect of the reversal-learning paradigm was a dominant response was overridden by an alternative due to changes of feedback contingencies. Previous studies evident the

PFC region played an essential role of this complex behaviour (Clark, Cools, &Robbins, 2004; Fellows and Farah, 2003; Hornak, O'Doherty, Bramham, Rolls, Morris, Bullock, & Polkey, 2004). South et al. (2014) recruited children with ASD and conducted a reversal-learning paradigm that accompanied with a surprising air puff as Pavlovian fear conditioning. After the reversal of cue contingencies, where a previously safe cue switched to air puff threat, only the controls but not the ASD children responded more strongly to the new threat cue. Critically, the performance of reversal learning in the ASD group was negatively correlated with symptoms of behavioural inflexibility. Evidence from neuroimaging studies revealed that both the ID/ED shift test and the reversal learning tests were involved with the OFC and/or the lateral PFC region (O'Reilly, Noelle, Brayer, & Cohen, 2002; Hampshire et al., 2012). This observed function-structure relationship in functional studies was consistent with the significant correlation we found between consistency score and the GM volume in the lateral OFC region. In the referential judgment test, ASD subjects were required to construct their internal hierarchy based on either self-related personality or self-unrelated weight of bottle water. During the trial-by-trial progress of the test, regardless of condition, subjects needed to override the existing hierarchy and fixated on the updated top-ranked item to get a higher consistency score. ASD individuals were diagnosed to have repetitive mannerism and/or restricted interest. As a result, if consistency score measured cognitive flexibility, we hypothesised to observe higher consistency score in both conditions in the ASD group than the baseline performance established by the TD group. On the other hand, referential judgements in the personality condition required self-referential processing, but not in the weight condition. If consistency score was able to capture different referential decision with and without the construct of self, we hypothesised that ASD adults would have selective impairments on the condition requiring self-referential decision (e.g., the personality condition), but intact performance compared with the baseline established by the TD group in the weight condition. Furthermore, in the gambling test chapter, ASD subjects demonstrated a dynamic change over time on the response speed under uncertain risky situations. In the referential judgment test, decision could be made based on the established internal hierarchy using self-related and self-unrelated constructs. It is possible that a similar dynamic change on response speed would manifest on a temporal scale in later trials as the test progressed. Therefore, we hypothesised that ASD subjects would demonstrated different response speed in the later stage of the test compared with TD subjects.

4.9 Behavioural result between the ASD and the TD groups

The ranking scheme in the ASD group

To compare the difference of the ranking scheme between conditions in the ASD group, the top-ranked item in the personality and the weight conditions of each ASD subject was first identified (see Table 4.5 and Figure 4.5 for illustration). In the personality condition, the item ranked at the top varied between ASD subjects, as the TD group did. For example, each of the twelve options was ranked as the top item at least once, and the number of ASD subject for each top-ranked item was ranged from 2% to 24% of the 34 ASD subjects. In the weight condition, the top-ranked item was clustered at one particular item. Similar as TD subjects, 55% of the ASD subjects considered a ‘ketchup’ bottle had the most similar weight as bottle water, and four items were never ranked the top.

Table 4.5. The frequency and proportion to the top-ranked faces in the personality condition, and the top-ranked object in the weight condition between each ASD subjects.

Personality condition			Weight condition		
Face no.	Frequency	Proportion	Object no.	Frequency	Proportion
1	4	0.10	1	1	0.02
2	3	0.07	2	0	0.00
3	5	0.12	3	0	0.00
4	1	0.02	4	0	0.00
5	10	0.24	5	3	0.07
6	2	0.05	6	0	0.00
7	3	0.07	7	24	0.55
8	3	0.07	8	2	0.05
9	2	0.05	9	4	0.09
10	1	0.02	10	3	0.07
11	3	0.07	11	2	0.05
12	4	0.10	12	5	0.11

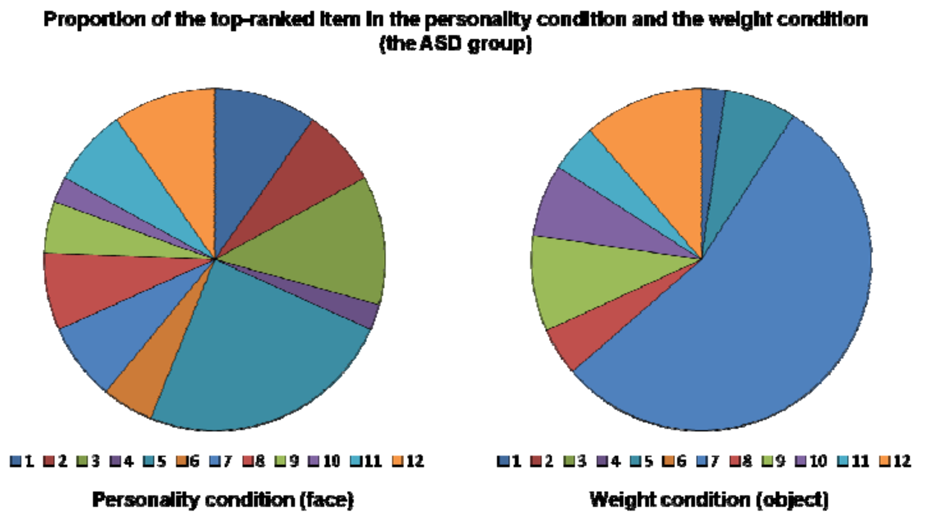


Figure 4.5. The ranking scheme of the ASD group in the personality (left) and the weight condition (right). In the personality condition, the items were faces with neutral expressions, and daily objects in the weight condition.

Between-group effects

The behavioural result of the ASD group, as well as the ‘baseline’ performance established by the TD group, were summarised in Table 4.6.

Table 4.6. The mean and standard deviations of consistency score and the overall reaction time (msec.) between conditions in the referential judgment test of the TD and the ASD groups.

	TD		ASD	
	mean	SD	mean	SD
Personality condition				
Consistency score	8.46	1.38	8.68	1.45
Reaction time (msec.)	1946.5	1080.7	2725.9	1255.7
Weight condition				
Consistency score	9.01	1.43	9.29	1.43
Reaction time (msec.)	1560.6	553.0	2132.9	784.2

Repeated measures ANOVA on consistency score showed a significant main effect of condition ($F(1,139)=12.362$, $p=0.001$), where the consistency score was significantly higher in the weight condition than in the personality condition. No significant effect of group ($F(1,139)=1.270$, $p=0.262$) and condition x group interaction ($F(1,139)=0.040$, $p=0.842$) was found. Repeated measures ANOVA on overall reaction time identified a significant main effect of condition ($F(1,139)=27.140$, $p<0.001$), which showed that response speed was significantly faster in the weight condition than in the personality condition. The analysis also found a significant main effect of group ($F(1,139)=19.833$, $p<0.001$), where ASD subjects responded significantly slower than TD subjects. No significant condition x group interaction was found ($F(1,139)=1.214$, $p=0.272$).

Temporal change on response speed

In order to examine if the decision-making processes underlie the referential judgment test had similar temporal change observed in the gambling test, where the acceleration rate differed between TD and ASD subjects, we conducted a repeated measures ANOVA with ‘stage’ as an additional within-subject factor. The reaction time for the first 33 trials was categorised as the early stage, and the later 33 trials were categorised as the late stage (see Table 4.7 for summary). First repeated measures ANOVA showed a significant main effect of stage $(F1,139)=132.890$, $p<0.001$), where the response speed accelerated in the later stage than in the early stage. Next we examined all the stage-related effect. Repeated measures ANOVA did not find a significant condition x group x stage interaction ($F(1,139)=0.046$, $p=0.830$). However, a marginal significant group x stage interaction ($F(1,139)=3.879$, $p=0.051$) was observed, and follow-up analysis showed that the acceleration (mean reaction time in the later stage minus mean reaction time in the early stage) was higher in the ASD group (mean difference: 782.38 msec.) than in the TD group (mean difference: 554.06 msec., $t(139)=1.969$, $p=0.051$) (see Figure 4.6).

Table 4.7. The reaction time in the early and the late stages in the personality and the weight conditions between the ASD and the TD groups.

	TD		ASD	
	mean	SD	mean	SD
Personality condition				
Reaction time (msec.) - Early stage	1933.8	973.2	2785.7	1650.9
Reaction time (msec.) - Late stage	1368.7	837.3	2012.2	1114.7
Weight condition				
Reaction time (msec.) - Early stage	1651.7	913.0	2197.0	995.5
Reaction time (msec.) - Late stage	1108.7	469.2	1405.7	611.0

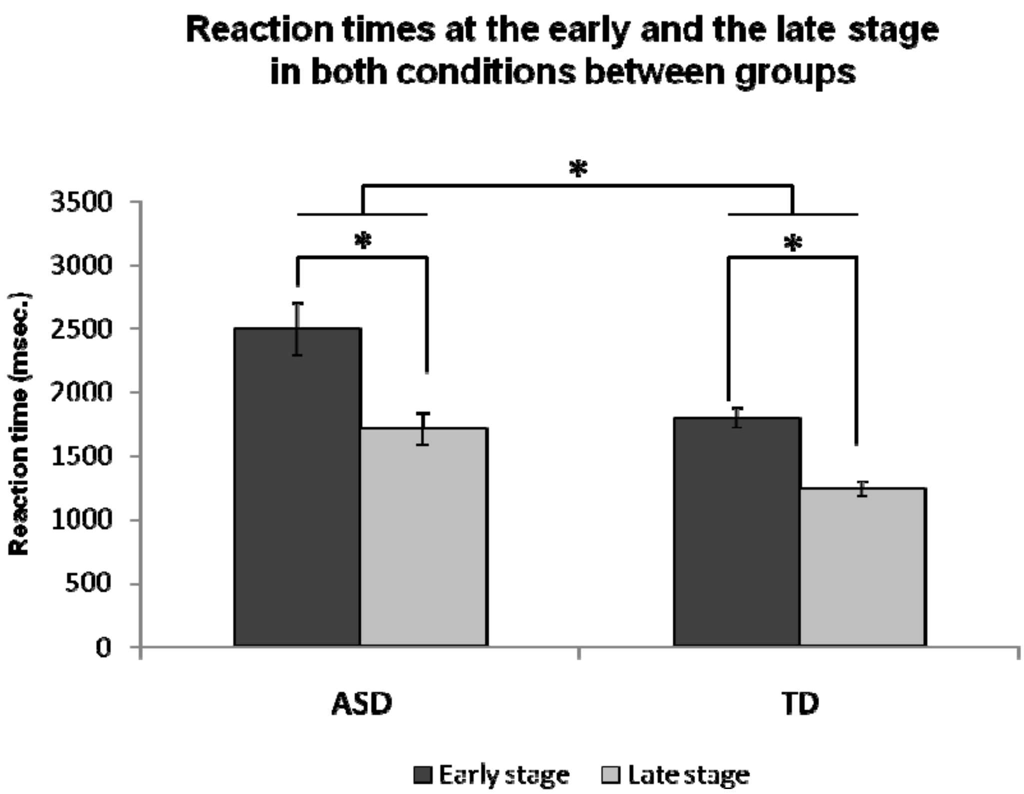


Figure 4.6. The acceleration of the reaction time between conditions was significantly higher in the ASD group than the TD group.

4.10 Discussion of the behavioural result between the ASD and the TD groups

The referential judgment test examined the decision-making processes based on judgments with or without self-referential components. First, the analysis on the ranking scheme found similar pattern as identified in the TD group, where the distribution of the top-ranked item was distinct between the personality and the weight conditions. This result demonstrated that the establishment of the internal hierarchy during referential judgment amongst ASD subjects was similar as TD subjects. In the previous sections, baseline behavioural performance established by the TD group and the neural correlates demonstrated by the TD sub-group showed that the consistency score in the current study did not directly measure self-referential processes, but mental processes relating to cognitive flexibility instead. The core feature that distinguished processing using self-related from self-unrelated constructs might be eliminated due to the scoring mechanism we implemented, or was unable to observe due to the facet of structural-based analysis instead of functional one. Repeated measures ANOVA failed to identify significant main effect of group, or condition x group interaction on consistency score, which indicated that no deficit relating to cognitive flexibility was found in the ASD group. However, it is interesting to note that the raw consistency score in both conditions were actually higher in ASD subjects than in TD subjects. This raised a possibility that the impairments found in ASD subjects in previous studies, e.g., ASD studies using the ID/ED test and the reversal learning tests, did not measured the same underlying process identified in the current study. Instead, it is possible that it was the repetitive mannerism or the rigid behavioural interests of ASD subjects that contributed to the enhanced, yet not significant, consistency score. In order to have higher consistency score, as discussed earlier in the VBM section, subjects needed to override existed contingency of the internal hierarchy. However, after identifying the top-ranked item, or the higher-ranked item amongst the two options, subjects who were able to fixate to it would show more consistent decisions, and subsequently led to higher consistency score. The consistency score using complex Repertory Grid approach not only failed to tap on the difference between self-related and self-unrelated processing, but also introduced other complicated sub-processes associated with cognitive flexibility.

Analysis on overall reaction time revealed a main effect of group, which showed that ASD subjects responded significantly slower than TD subjects did. This was consistent with the robust response slowness reported in previous ASD studies (Ozonoff et al., 1994; Rinehart, Bradshaw, Brereton, & Tonge, 2001; Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004; Schmitz, Daly, & Murphy, 2007), which was considered as an index of cognitive inflexibility. Due to the identified compensation on reaction time amongst ASD subjects in the later stage of the loss condition in the gambling test, we also investigated the temporal change on reaction time as the test progressed in the referential judgment test. Repeated measures ANOVA revealed a marginal significant group x stage interaction, which showed that, when collapsing two conditions, higher acceleration in the later stage was observed in the ASD group than in the TD group. ASD subjects seemed to 'catch up' with TD subjects in the later stage of the test, which was the period of time that the internal hierarchy was gradually established and a certain ranking scheme was ready to follow. However, independent t test revealed that TD subjects still responded significantly faster than ASD subjects in the later stage ($t(139)=3.957$, $p<0.001$). Therefore, it is possible that the marginal group x stage interaction was driven by a ceiling effect, where the ASD subjects had more ‘room’ to accelerate than the TD subjects in the later stage of the test. Taken together, the result raised an interesting direction on measuring the repetitive mannerism in ASD subjects, which involve the consistency of fixating to the preferred option, and subsequently resulted in dynamic change of response speed on a temporal scale. Specifically, this dynamic change on reaction time was usually ignored or overlooked by using averaged scores, which was similar as taking one single snapshot of sequential moves. This ‘averaging artefact’ has been proposed in behavioural experiments which showed that systematic pattern of inter-individual differences were sometimes ignored and can be dissociated from averaged activities (see illustration in Kanai & Rees, 2011). It is therefore important to examine decision-making process on a temporal scale to recognise this ‘temporal averaging artefact’, especially in ASD research where repetitive mannerism, a feature that required multiple exposure of the same option, is inherently more prominent over time.

Chapter 5. PFC battery: the video mentalizing test

5.1 Measurements for understanding other's mind using video varying in intentionality and complexity

Making decisions under risky situations or evaluating self-referential thoughts could be complex enough mental processes in our daily lives. However, it is even more overwhelming for people to make inter-personal decisions, rather than making decisions on their own, while interacting with other individuals. The ability to process complex social information, e.g., making inferences to others' states of mind, or based on subtle cues like facial expression, voice tones, or body movements is essential for social interaction. In cognitive psychology, the term 'Theory of Mind (ToM)' refers to the kind of ability to make inferences to other's intentions, beliefs, desires or wishes (Frith and Frith, 2006). Previous studies using lesion and functional neuroimaging approaches demonstrated that the PFC region played an important role in ToM processing (Stone, Baron-Cohen, & Knight, 1998; Stuss et al., 2001; Gallagher, Jack, Roepstorff, & Frith, 2002). Psychological tests like the 'Sally and Anne' test (Baron-Cohen, Leslie, & Frith, 1985) was a classic example for ToM tests. In order to perform accurately in the test, subjects are required to 'put oneself in other's shoes' by experiencing a situation from other's perspective, and make correct inferences to other's belief. In ToM studies, different psychological paradigms designed to measure ToM competence employ a variety of experimental materials. For example, the 'Reading the Mind in the Eyes' test developed by Baron-Cohen, Jolliffe, Mortimore, and Robertson (1997) used pictures of eyes as stimuli, and required subjects to make inferences about others' mental states from viewing photographs of others' eyes. Besides using static stimuli as pictures, other paradigms like ‘the Awkward Moments’ test (Heavey, Phillips, Baron-Cohen, & Rutter, 2000) used commercial videos, which combined both visual and auditory inputs to depict scenarios that were more realistic to subjects. An important advantage of using videos as stimuli is that they provide opportunities to create natural scenes that included subtle, transient social cues, like actual daily situations. Nevertheless, it is possible that using commercials as experimental stimuli, like the Awkward Moments Test, might involve too exaggerated social interactions created from uncommon or unrealistic scenarios. In order to control for this potential unrealistic effect, Golan, Baron-Cohen, Hill, and Rutherford (2007) developed a ‘Reading the Mind in Films’ (RMF) test, which consisted of short scenes taken from feature films relating to everyday lives. Despite the advantage of video film stimuli simulating real-life scenarios, a possible confound that co-exists in both ‘the Awkward Moments’ test’ and the RMF test occurs in the testing phase. In both paradigms, the questions proposed to subjects during the testing phase consist of emotional adjectives, like ‘embarrassed’, ‘shocked’, or ‘awkward’. The implementation of emotional adjectives as measurements for ToM-related ability might introduce unexpected variations, e.g., different understanding of the emotional adjectives leading to different interpretations of the questions between individuals. Moreover, using emotional adjectives could be instructive to subjects in some senses. For example, when instructed ‘don’t think of an elephant’ usually led to subjects start thinking of an elephant instead. It is therefore possible that using emotional adjectives as the testing options (e.g., the Awkward Moments Test, Heavey et al., 2000) would guide subject’s mental status in an instructive way, instead of solely relied on mind-reading ability.

In order to control for the potential confounds described above, we developed a video mentalizing test by making modifications to both experimental stimuli and testing questions. The video mentalizing test, as the RMF test, used short video clips as experimental stimuli, and we further categorised the videos along two diagonal dimensions, the level of ‘intentionality’ and ‘complexity’. The level of intentionality in video clips was determined by the principle proposed by Castelli and colleagues (2000; 2002), where the materials for measuring ToM ability were rated on a 0-5 point scale. The social behaviours rated by a score of 0-3 points referred to the actions that were non-deliberate in nature, or without response to other’s action. The social behaviours rated by a score of 4-5 points referred to deliberate actions in response to other’s mental state or with the goal of affecting other's mental state. Following this principle, the videos involved high level of intentionality, where scenarios depicting behaviours rated 4-5 in Castelli et al. (2000; 2002) and subjects were required to make inferences to the character’s mental state, were labelled as ‘high-mentalizing’ videos. In comparison, the videos that involved low level of intentionality, where scenarios depicting behaviours rated 0-3 in Castelli et al. (2000; 2002) and subjects were required only to understand the scene without inferring character’s feeling and mental states, were labelled as ‘low-mentalizing’ videos. Apart from the level of intentionality of the videos, we also categorised the video materials along a ‘complexity’ dimension, which differentiated the amount of social information required to process. Previous ToM studies had implemented different number of characters in the depicted social interaction, e.g., two characters were involved in the ‘Sally and Anne’ test, multiple characters were involved in the ‘Awkward Moments Test’, and 1-4 characters were involved in the RMF test. It is therefore possible that the number of characters might introduce a systematic effect in ToM performance due to appearance of interactions, which were supposed to involve at least two characters, and more characters involved in the social scenarios would increase the amount of social information. Accordingly, in our video mentalizing test, half of the videos, regardless of the level of intentionality, involved only two characters and the other half involved more than two characters. Following the speculation described above, we labelled the videos depicting social interaction between two characters as ‘dyad’ videos, and the videos depicting social interaction between more than two characters as ‘group’ videos. As a result, the video mentalizing test involved a 2 x 2 design between two levels of intentionality and two levels of complexity, which led to four conditions of the videos including high-mentalizing + dyad (HD), high-mentalizing + group (HG), low-mentalizing + dyad (LD), and low-mentalizing + group (LG).

Besides the 2 x 2 design in experimental materials, we also manipulated the structure of the questions during the testing phase. In order to control for a potential confound by using emotional adjectives, we employed the same neutral question in every question and structured the question in a systematic way. In previous ToM studies, ToM competence was measured by accuracy, in an all-or-nothing fashion, but it seems perhaps unnatural to dichotomize the ToM ability between individuals as either ‘capable’ or ‘incapable’ of making correct inferences of other’s intentions. Therefore measuring ToM competence in a continuous way might provide further insights on this essential ability. In order to examine this possibility, we used multiple choices questions (MCQs) to measure ToM ability between individuals. Each MCQ consisted of four options, and each option varied in four levels of ‘appropriateness’ (Castelli, Happe, Frith, & Frith, 2000). The ‘correct’ response meant that subjects made correct inferences about the intentions or emotional states of the characters. The ‘plausible’ response meant that subjects made inferences about the intentions or emotional states of one of the characters as well, but based on the information that were not central to the scene. The ‘incorrect’ response meant that subjects made incorrect inferences to the intentions or emotional states of one of the characters. The ‘irrelevant’ response meant that subjects described statements that included only key words from the scene and/or misunderstood the character’s mental states. To quantify this appropriateness, a weighted score scheme was calculated: correct->4, plausible->3, incorrect->2, irrelevant->1, and no response->0. The higher the weighted appropriateness referred to better understanding of other’s mind, and provided a potential scope to examine ToM capability in a continuous way. The aim of the current chapter was to establish the baseline performance of the video mentalizing test. As a result, we focused on examining the effect between intentionality x complexity in the four kinds of video conditions (HD, HG, LD, LG conditions). We further investigated if measurements addressing ToM competence differed using an all-or-nothing variable (e.g., accuracy) and a continuous index (e.g., appropriateness). The response speed for making decisions in each video condition was also analysed.

5.2 Methods of the video mentalizing test

<u>Materials and Design</u>

The video mentalizing test was displayed on DMDX experimental software (Forster & Forster, 2003) and consisted of fourteen coloured short video clips taken from the BBC television programme. Two of the fourteen video clips were used for practice, and the other twelve were used for experimental stimuli. The video clips included both visual inputs (facial expression, body language, and physical interactions) and auditory inputs (verbal content, and intonation changes) depicting various kinds of social interactions. The video clips can be categorised into four conditions: high mentalizing dyad (HD), high mentalizing group (HG), low mentalizing dyad (LD), and low mentalizing group (LG), according to the level of intentionality (Castelli et al., 2000, 2002) and complexity differed in the numbers of characters involved. For videos varying in levels of intentionality, the high-mentalizing videos depicted social situations that characters making inferences to others minds under a various kinds of contexts, e.g., a mother made poor excuses for not attending her daughter’s important event, an employer tried to be nice when firing his employee, a female tended to flirt with her new collegue, or love affairs between two boys and one girl. The low-mentalizing videos demonstrated daily situations that characters discussing some facts or exchanged information without making inferences to others’ minds, e.g., a policeman checked the license of a driver, a show host asked the recipe of Malteese pie, two men disussed the function of Victorian theatre, or a secretary helped two visitors arranging evening schedules. For videos varying in complexity, only two characters were included in dyad videos, whereas there were more than two characters involved in group videos. Two MCQs were asked for each video clip using the standard question ‘Which of these statements best describes the situation you have just seen?’ followed by four possible options varying in four levels of appropriateness. All the options in the MCQs were matched for sentence length and readability between conditions (see Figure 5.1). In the video mentalizing test, each condition contained three video clips, along with six MCQs. The order of the video clips was counterbalanced using a Latin-Square design and was identical across all subjects. The position of the correct answer in each MCQ was also counterbalanced. A threshold for maximum reaction time (RT) was set to two standard deviations above the mean (Max RT = 27000ms) from the pilot study.

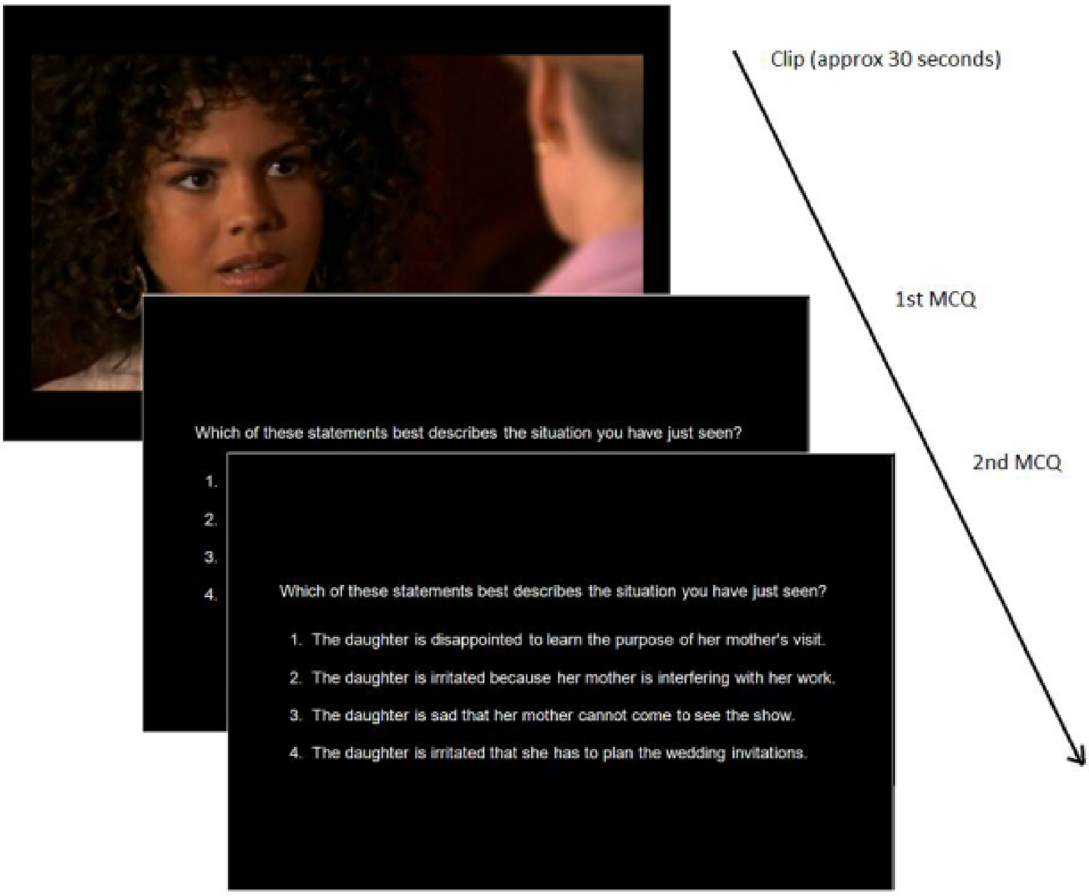


Figure 5.1. The experimental procedure of the video mentalizing test, where each 30 second video clip was accompanied with two MCQs that varied with level of appropriateness.

<u>Procedure</u>

At the beginning of the video mentalizing test, participants were given instructions for keypress and two videos along with four MCQs for practice. Subjects were instructed to choose the option best describing the scene depicted in the video and made a decision using the corresponding 1, 2, 3, 4 keys. There was a 3 second countdown and a fixation cross presented before the presentation of each video clip for subjects to prepare themselves. After the presentation of each video, the first

MCQ appeared on the screen for 27000 milliseconds. If the maximum reaction time expired, a sign saying, “Time is up!” was displayed for 300 milliseconds on the screen and the next question appeared. Otherwise, the second question was presented after a response was registered. Subjects were required to wear headphones throughout the video mentalizing test, and were allowed to adjust the volume to the comfortable level. The video mentalizing test took each subject around 20 minutes to administer. The responses and the reaction times to each MCQ were recorded. Only the valid trials with a response registered within the time threshold were included and analysed. The weighted score based on the appropriateness of each option was also calculated.

5.3 Behavioural result of the TD group

The accuracy, appropriateness and reaction time for each condition were entered into repeated measures ANOVA with intentionality (high vs. low) and complexity (dyad vs. group) as within-subject factors. The behavioural result of accuracy, appropriateness, and reaction time in each condition were summarised in Table 5.1.

Table 5.1. The mean and standard deviation of accuracy, appropriateness, and reaction time (msec.) between conditions in the video mentalizing test of the TD group. Left panel: the result in each condition; Right panel: the main effect of intentionality and complexity separately.

		mean	SD		mean	SD
Accuracy						
	HD videos	0.77	0.16	High-mentalizing	0.74	0.13
	HG videos	0.70	0.20	Low-mentalizing	0.72	0.15
	LD videos	0.85	0.16	Dyad conversation	0.81	0.12
	LG videos	0.60	0.22	Group conversation	0.65	0.17
Appropriateness						
	HD videos	3.62	0.36	High-mentalizing	3.51	0.32
	HG videos	3.40	0.47	Low-mentalizing	3.49	0.32
	LD videos	3.71	0.34	Dyad conversation	3.66	0.28
	LG videos	3.27	0.45	Group conversation	3.34	0.37
Reaction time (msec.)						
	HD videos	10730.7	2933.6	High-mentalizing	12013.9	2749.8
	HG videos	13297.1	3077.4	Low-mentalizing	11068.8	2478.0
	LD videos	10549.0	2751.2	Dyad conversation	10639.9	2704.6
	LG videos	11588.6	2487.7	Group conversation	12442.8	2591.7

Between-condition effects

Accuracy

Repeated measures ANOVA on accuracy revealed a significant effect of complexity ($F(1,102)=96.018$, $p<0.001$), which showed that accuracy for dyad videos was significantly higher than for group videos. The result also revealed a significant intentionality x complexity interaction ($F(1,102)=31.079$, $p<0.001$). Follow-up analysis confirmed the interaction by showing higher complexity effect in low-mentalizing videos (mean difference=0.25) than in high-mentalizing videos (mean difference=0.07).

Appropriateness

Repeated measures ANOVA on appropriateness demonstrated a significant effect of complexity ($F(1,102)=84.461$, $p<0.001$), which showed that appropriateness for dyad videos was significantly higher than for group videos. Similar to analysis on accuracy, a significant intentionality x complexity interaction ($F(1,102)=9.968$, $p=0.002$) was also identified on appropriateness. Follow-up analysis revealed that the interaction was driven by a higher complexity effect in low-mentalizing videos (mean difference=0.43) than in high-mentalizing videos (mean difference=0.22).

Reaction time

Repeated measures ANOVA first identified a significant effect of intentionality ($F(1,102)=50.171$, $p<0.001$) and of complexity ($F(1,102)=134,309$, $p<0.001$), where response speed was significantly faster for low-mentalizing than for high-mentalizing videos, as well as faster for dyad than for group videos. The result also found a significant intentionality x complexity interaction ($F(1,102)=30.976$, $p<0.001$). Follow-up analysis confirmed the interaction by revealing a higher intentionality effect for group videos than for dyad videos.

Correlation analysis

Spearman's rank-order correlation analysis was conducted in two different approaches. In the first approach, we focused on the within-variable effect, where the relationships on accuracy, appropriateness, and reaction time between the four experimental conditions (HD, HG, LD, LG) were examined. In the second approach, we then analysed the between-variable effect, where the relationships between the four experimental conditions using accuracy and reaction time were examined separately.

In the first approach, correlation analysis revealed positive significant relationships of accuracy between HG vs. LG, and LD vs. LG (all $p<0.05$), but not for other pairwise combinations. Analysis of appropriateness found positive significant correlations between HG vs. LG, LD vs. LG, and LD vs. HG (all $p<0.05$), but no significant correlations were found between other combinations. Spearman's rank-order correlation analysis on reaction time found positive significant relationships between response speed for all pairwise combinations (all $p<0.001$). In the second approach, significant relationships were found between accuracy, appropriateness, and reaction time for HD videos (all $p<0.01$), HG videos (all $p<0.01$), LD videos (all $p<0.01$ except for accuracy and reaction time $p=0.058$), and LG videos (all $p<0.01$). Notably, all the correlations were in a positive way between accuracy and appropriateness, yet in a negative way between reaction time vs. accuracy, as well as in reaction time vs. appropriateness.

5.4 Discussion of the behavioural result in the TD group

The video mentalizing test measured ToM competence using short videos depicting daily social interaction. For the experimental stimuli, we further categorised the videos along two orthogonal dimensions, an intentionality aspect that differed in levels of mentalizing, and a complexity aspect that differed in amount of social information involved. For the testing phase, we controlled the structure of the question and further analysed the appropriateness of the responses according to a weighted score in a continuous fashion. In this section, the aim was to establish a ‘baseline’ performance for the video mentalizing test, and explored the effect of intentionality and complexity to ToM performance, as well as the potential difference when using appropriateness to measure ToM competence.

Repeated measures ANOVA identified a significant main effect of intentionality only in reaction time, which showed that the response time was significantly longer for high-mentalizing videos than for low-mentalizing videos in TD subjects. The null effect of intentionality on accuracy and appropriateness indicated that TD subjects did not find videos requiring higher intentionality more difficult than lower intentionality items. Nevertheless, TD subjects took significantly longer to make decisions to high-mentalizing videos, which suggested more mental processing is involved when making inferences to other’s minds. Repeated measures ANOVA on accuracy, appropriateness, and reaction time all revealed significant main effects of complexity, where TD subjects responded more accurately, more appropriately, and responded faster for dyad videos than for group videos. This implies that the number of characters involved in the conversation has a strong impact on ToM competence. A possible explanation of this effect is the amount of social information required to process, where videos involving conversation between more than two characters supposedly contains more information for subjects to process than videos involving conversations between only two characters. Nevertheless, the link between the number of characters and the amount of social information requires more examination to validate. It is possible that more characters involved in a social interaction do not necessarily create more social information to process, and other factors including the nature of context or the characters involved might be influential for the effect. For example, two politicians making sarcastic statements toward each other during a live national talk show might create a more complicated social scenario than four Amish people planning a surprise party for their close friends in a peaceful village. Another possible explanation of this complexity effect on all three variables involves distracted attention, e.g., social scenarios involving more than two characters would inevitably lead to more distraction or more changes of eye gaze when switching amongst characters. It is also possible that the implementation of recorded videos, despite depicting real-life social interaction, was not ecological enough to simulate actual overwhelming interpersonal communication. In ToM tests using videos as stimuli, the switch of camera controls the direction of eye gaze between characters, but in real-life situations, this direction of eye gaze is a voluntary move instead. For example, certain close-up scenes focusing on eyes would create similar effects as the ‘Reading the Mind in the Eyes test’, whereas an intense scene using a distant shot for cinematic purposes might hinder subjects from discovering the subtle yet crucial social cues on the characters. Further investigations are required to disentangle the effect of complexity contributed by the factors discussed above.

Repeated measures ANOVA also identified significant interactions between intentionality and complexity on accuracy, appropriateness, and reaction time. Follow-up analysis revealed that the superior performance for dyad over group videos was stronger in the low-mentalizing condition than the high-mentalizing condition. This indicates that the previously discussed effect of complexity had a stronger impact when lesser level of intentionality was required. If the effect of complexity resulted from the restriction of camera, then this cause originated from the nature of experimental stimuli and should have an equivalent effect on both high-mentalizing and low-mentalizing videos. On the other hand, if the effect of complexity came from the difference in social information, given that high-mentalizing involved far more complex scenarios than low-mentalizing videos, it seems possible that TD subjects were engaged in ToM-related processing and this diminished the effect of complexity in a more overwhelming situation. Analysis of reaction time also found a significant intentionality x complexity interaction. Follow-up analysis demonstrated that the effect of intentionality made much more impact on group videos than on dyad videos. A possible explanation is that under social situations involving a larger amount of social information, subjects will take longer to decipher and make inferences about other's minds, but find it relatively easier under situations that contained lesser amount of social information.

Correlation analyses of within-variable effects revealed several positive significant relationships between different conditions. Analysis of reaction time revealed strong positive correlations between all kinds of videos. This raises a possibility that there was a 'general' competence on ToM-related processing speed, where the boundary between varying levels of intentionality and complexity was vague, or further suggests a continuous spectrum. For the between-variable effect, the positive correlations between accuracy and appropriateness for all kinds of videos suggested that there was no fundamental difference between measuring ToM competence using an absolute accuracy or continuous measure of appropriateness. On the other hand, reaction time was found to negatively correlate with both accuracy and appropriateness in all four kinds of videos. This indicates that spending a longer time making decisions to social interactions did not accompany better performance as suggested by the classic 'speed-accuracy trade-off', but led to worse performance instead in the video mentalizing test. This result might suggest that mentalizing ability might be a rather intuitive cognitive process, where longer consideration would elicit other ToM-unrelated processes and subsequently brought more errors instead.

5.5 Neuroimaging findings of mentalizing ability varying in intentionality and complexity

The ability to understand other people's mental states or make inferences from other's perspective is referred as mentalizing, which requires theory of mind (ToM). Previous functional neuroimaging studies have established a robust link between different mentalizing tests and the medial PFC region (see Frith & Frith, 2006). For example, Gallagher et al. (2002) used the 'stone, paper, scissors' game to simulate on-line interactions with another person comparing with control conditions. Their result revealed only the medial PFC region was more activated when making intentional stances and evident the linkage between the medial PFC region and making attributions about other's mental states. In another functional study of mentalizing, Castelli et al. (2000) used animations of geometric shapes as stimuli to simulate mental state attribution, and subjects were required to watch the 'interactions' between the shapes passively. The result found increased activation in the medial PFC region, which highlighted an important notion that the ability to make inferences of other's mind was originated from making inferences of abstract actions, even when passively viewing movements for non-living objects. As described earlier, the nature of the experimental stimuli varied between different ToM tests, e.g., pictures of the eyes in Baron-Cohen et al. (1999), verbal stories in Fletcher, Happe, Frith, Baker, Dolan, and Frackowiak (1995), non-verbal cartoon stories in Brunet, Sarfati, Hardy-Bayle, and Decety (2000), and verbal and non-verbal stories in Gallagher, Happe, Brunswick, and Fletcher (2000). It is critical to observe that, regardless of the nature of experimental materials used in ToM tests, neural activity in mentalizing conditions has been reported consistently in the medial PFC.

Nevertheless, several other brain regions are frequently observed in mentalizing tests as well. For example, Britton, Phan, Taylor, Welsh, Berridge, and Liberzon (2006) used video films differing along sociality (non-social vs. social) and valence (positive vs. negative) dimensions to compare different regional coding of brain activations. The result revealed that social positive videos that associated with joy activated the medial OFC region (peak MNI coordinate: 15, 60, -12), which suggested the involvement of emotional valence during social processing in the medial OFC region. In order to directly contrast emotional perspective-taking versus cognitive perspective-taking, Hynes, Baird, and Graftonl (2006) used written scenarios developed by Fletcher et al. (1995) to investigate the functional role of the OFC involved in ToM tests. The result showed that, despite the medial PFC activated in both cognitive and emotional perspective-taking contrasts, the medial OFC (included both BA11 and BA25 regions) was preferentially involved with emotional rather than cognitive perspective-taking, which revealed that distinct functional sub-components are associated with ToM-related processing. Other techniques have been introduced to investigate the sub-components that supported mentalizing. For example, Hampton, Bossaerts, and O'Doherty (2008) used a model-testing approach to investigate the computations underlying mentalizing, which included measurements to the associations between neural activities in different parts of the mentalizing network and different cognitive components. The result showed that the signals in a sophisticated 'influence' model, which simulated not only tracking other's actions but also incorporating knowledge of how one's own actions influenced the other's strategy, significantly correlated with neural activities in the medial PFC, as well as the medial OFC region. Together these findings highlight that the cognitive processes relating to ToM elicit a network including not only the medial PFC region, but also the OFC region that is associated with emotional components.

In the current video mentalizing test, the short videos were categorised along two orthogonal dimensions, the intentionality (high- and low-mentalizing) and the complexity (dyad and group conversations). Subjects were required to answer the same question ‘which of these statements best describes the situation you have just seen?’, and made decisions from four options varying in appropriateness. Along the intentionality dimension, to have better performances for high-mentalizing videos, subjects needed to understand and make correct inferences of the character’s mind, whereas to have better performances for low-mentalizing videos, it did not necessarily require the ability to make correct inferences of the character’s mind. Along the complexity dimension, to have better performances for group videos, subjects needed to process social information based on interactions between more than two characters, whereas to have better performances for dyad videos, subjects only needed to process fewer amount of social information based on interactions between only two characters. Previous functional studies measuring mentalizing ability demonstrate a function-structure relationship between ToM competence and different PFC sub-regions along the medial line (BA9, 10, 11, and 25). As a result, the aim of this VBM regression analysis was to examine the distinct correlations between behavioural performance in different conditions and different PFC sub-regions. For the videos varying in intentionality, we hypothesised that the GM volume along the medial line of the PFC would correlate with the performance relating to high-mentalizing videos, but not to low-mentalizing videos. For the videos varying in complexity, we hypothesised that the GM volume along the medial line of the PFC would correlate with performance for both dyad and group videos, given that the scores for dyad and group videos both involved understanding the character's mental states.

5.6 Behavioural and VBM result of the TD sub-group

Behaviour investigation into the video mentalizing test

The accuracy, appropriateness and reaction time for each condition were entered into repeated measures ANOVA with intentionality (high vs. low) and complexity (dyad vs. group) as within-subject factors. The behavioural part of the result, including accuracy, appropriateness, and reaction time in each condition are summarised in Table 5.2.

Table 5.2. Accuracy, appropriateness, and reaction time (msec.) between conditions in the video mentalizing test of the TD sub-group (n=62). Panel (a): the result in each condition; panel (b): the main effect of intentionality and complexity.

(a)		mean	SD
Accuracy			
	HD videos	0.77	0.17
	HG videos	0.70	0.19
	LD videos	0.84	0.16
	LG videos	0.60	0.22
Appropriateness			
	HD videos	3.64	0.38
	HG videos	3.37	0.49
	LD videos	3.67	0.37
	LG videos	3.26	0.46
Reaction time			
	HD videos	11222.5	2883.2
	HG videos	13957.5	3115.0
	LD videos	11034.2	2645.7
	LG videos	12002.7	2504.3

(b)		mean	SD
Accuracy			
	High-mentalizing	0.73	0.14
	Low-mentalizing	0.72	0.15
	Dyad conversation	0.80	0.12
	Group conversation	0.65	0.16
Appropriateness			
	High-mentalizing	3.50	0.36
	Low-mentalizing	3.47	0.35
	Dyad conversation	3.65	0.31
	Group conversation	3.32	0.38
Reaction time			
	High-mentalizing	12590.0	2709.5
	Low-mentalizing	11518.4	2467.3
	Dyad conversation	11128.3	2584.2
	Group conversation	12980.1	2634.4

Accuracy

Repeated measures ANOVA found a significant main effect of complexity ($F(1,61)=49.016$, $p<0.001$), where subjects had better accuracy for dyad videos than for group videos. The analysis identified a significant intentionality x complexity interaction ($F(1,61)=17.239$, $p<0.001$). Follow-up analysis revealed that the interaction was driven by higher dyad vs. group difference in low-mentalizing videos (mean difference=0.233) than in high-mentalizing videos (mean difference=0.073). No significant main effect of intentionality was found ($F(1,61)=0.281$, $p=0.598$).

Appropriateness

Repeated measures ANOVA found a significant main effect of complexity ($F(1,61)=57.155$, $p<0.001$), where subjects responded more appropriately to dyad videos than group videos. No significant main effect of intentionality was found ($F(1,61)=0.628$, $p=0.431$). The intentionality x complexity interaction was not significant ($F(1,61)=3.120$, $p=0.082$).

Reaction time

Repeated measures ANOVA found a significant main effect of intentionality ($F(1,61)=31.418$, $p<0.001$), which revealed that subjects made decisions significantly more slowly to high-mentalizing videos than low-mentalizing videos. The analysis also revealed a significant main effect of complexity ($F(1,61)=90.928$, $p<0.001$), where subjects responded significantly slower for group videos than for dyad videos. A significant intentionality x complexity interaction ($F(1,61)=24.701$, $p<0.001$) was found. Follow-up analysis confirmed that the faster response speed for low-mentalizing videos than for high-mentalizing videos was more prominent in videos involved group conversation than in videos involved dyad conversation.

Correlation analysis

We used Spearman's rank-order correlation and followed the same procedure as in the TD group. In the first approach, correlation analysis of accuracy only revealed a positive significant relationship between LD vs. LG videos (r_s (62)=0.286, $p=0.024$), but not for other pairwise combinations. Analysis of appropriateness only identified a positive significant correlation between LD and LG videos (r_s (62)=0.290, $p=0.022$), but no significant correlations were found between other combinations. Spearman's rank-order correlation analysis of reaction time found positive significant relationships between response speed for all pairwise combinations (all $p<0.001$). In the second approach, significant relationships were found between accuracy, appropriateness, and reaction time for HD videos (all $p<0.05$), HG videos (all $p<0.05$), LD videos (all $p<0.05$), and LG videos (all $p<0.05$). The identified correlations were positive between accuracy and appropriateness, yet negative between reaction time vs. accuracy, and between reaction time vs. appropriateness as well.

VBM investigation into the video mentalizing test

The VBM part of this investigation is organised in two approaches. In the first approach, we explored the neural correlates associated with accuracy and appropriateness for each of the four kinds of videos, and the results were summarised in Table 5.3. In the second approach, given that a robust link between mentalizing ability and the medial PFC region has been established by previous functional neuroimaging, we further examined the correlation between the performance for the main effect of intentionality (high and low-mentalizing videos), as well as the complexity (dyad and group conversations), and the GM volume in the medial PFC region. The relationship between the performance for dyad and group conversations and the medial line of the PFC region was also examined for exploratory purpose (see Table 5.4).

Table 5.3. The VBM result of the video mentalizing test. The GM cluster in the PFC region showing significant correlations with the accuracy, appropriateness in the video mentalizing test between the four conditions (p<0.001, uncorrected for whole brain analysis, and p<0.05, FWE-corrected for SVC using different ROIs derived from the AAL atlas). Brodmann areas are approximate.

	p<0.001, uncorrected				SVC (FWE<0.05)	
	Whole brain analysis				AAL_Superior_Medial	
	k	t	MNI	Label	p	MNI
Accuracy for videos in different conditions						
High-Dyad	2947[a]	6.25	[0, 41, -24]	BA11	<0.001	
	93	4.20	[-11, 57, 18]	BA10	0.014	[-11, 57, 18]
	135	3.81	[-3, 33, 51]	BA8	0.042	[-3, 33, 51]
High-Group	10	3.42	[-6, 53, 16]	BA9		
Low-Dyad						
Low-Group	59	3.84	[0, 56, 25]	BA9	0.038	[0, 56, 25]
	45	3.72	[8, 48, 36]	BA8	0.041	[8, 48, 36]

[a] survived from small volume correction (SVC) at the whole brain level at p<0.001

Table 5.4. The VBM result of the video mentalizing test. The GM clusters in the PFC region showing significant correlations with the accuracy, appropriateness in the video mentalizing test between the main effect of intentionality and complexity (p<0.001, uncorrected for whole brain analysis, and p<0.05, FWE-corrected for SVC using different ROIs derived from the AAL atlas). Brodmann areas are approximate.

	p<0.001, uncorrected				Small Volume Correction (FWE<0.05)					
	Whole brain analysis				AAL_Superior_Medial		AAL_Cinculum_Ant_Right		BA25 (WFU_pickatlas)	
	k	t	MNI	Label	p	MNI	p	MNI	p	MNI
Accuracy for videos in different conditions										
High-mentalizing	198	4.63	[-5, 53, 16]	BA9	0.004	[-5, 53, 16]				
	66	4.39	[15, 33, 30]	BA32			0.024	[12, 33, 28]		
	24	3.46	[-12, 30, -30]	BA11					0.045	[-12, 30, -15]
Low-mentalizing										
Dyad conversation	12	3.48	[-15, 41, 16]	BA9						
	38	3.47	[12, 30, -15]	BA25					0.036	[12, 30, -15]
	29	3.35	[3, 39, -24]	BA11						
Group conversation	85	4.04	[-5, 51, 15]	BA9	0.023	[-5, 51, 15]				

Accuracy

VBM regression analysis found a significant positive correlation between the accuracy for high-mentalizing dyad videos and the GM volume in bilateral medial OFC (BA11) region that survived FWE correction at the whole brain level (peak MNI coordinate: 0, 41, -24, k=2947, p=0.001) (see Figure 5.2(a)). The accuracy of high-mentalizing dyad videos was also positively correlated with other medial PFC regions along the midline structure including BA10 (peak MNI: -11, 57, 18; SVC: AAL_Frontal_Superior_Medial_Left, p=0.014) and BA8 regions (peak MNI: -3, 33, 51; SVC: AAL_Frontal_Superior_Medial_Left, p=0.042)(see Figure 5.2(b), 5.2(c)). The accuracy for the high-mentalizing group videos was also positively correlated with GM volume in the dorsomedial PFC region at [-6, 53, 16] using a lenient threshold at p<0.001 uncorrected (SVC: AAL_Frontal_Superior_Medial_Left, p>0.05). A positive significant correlation was identified between accuracy for low-mentalizing group videos and the GM volume in the dmPFC region at [0, 56, 25] (SVC: SVC: AAL_Frontal_Superior_Medial_Left, p=0.038) and the GM volume in BA8 region at [8, 48, 36] (SVC: SVC: AAL_Frontal_Superior_Medial_Left, p=0.041) (see Figure 5.2(d), 5.2(e)). No significant correlation was found between the accuracy for low-mentalizing dyad videos and any GM volume in the medial PFC region.

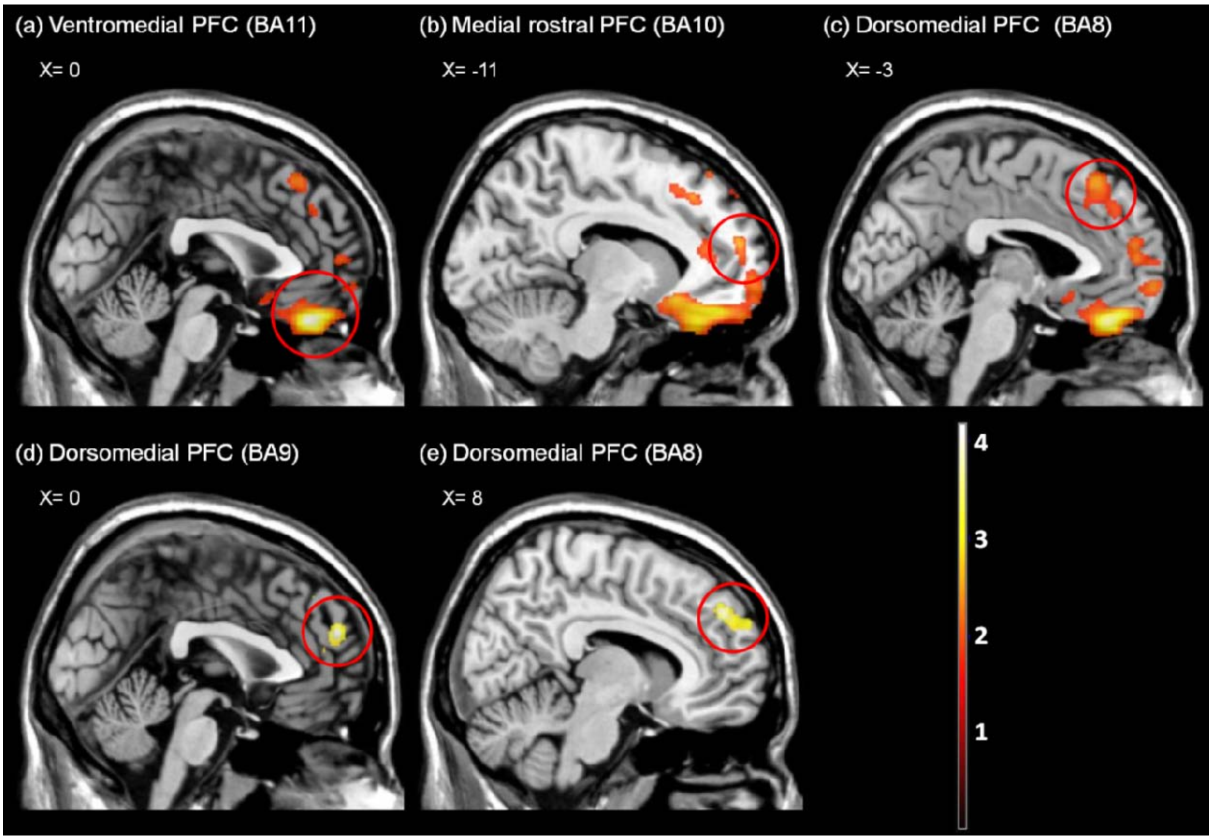


Figure 5.2. The GM volume that significantly correlated with the variables in the video mentalizing test. Accuracy for the high-mentalizing+dyad (HD) videos was positively correlated with a GM cluster located in the ventromedial PFC region (panel a), a GM cluster in the medial rostral PFC region (panel b), and a GM cluster in the dorsomedial PFC region (panel c). Accuracy for the low-mentalizing+group (LD) videos was positively correlated with a GM cluster in the dorsomedial PFC region approximately in BA9 (panel d), and a GM cluster in the dorsomedial PFC region approximately in BA8 (panel e).

In the second part of the VBM analysis, we examined the relationship between the GM volume in the medial PFC region and the main effects of intentionality and complexity separately. VBM regression analysis revealed a significant positive correlation between accuracy for high-mentalizing videos and the GM volume along the midline structure of the PFC region, including the dorsomedial PFC region at [-5, 53, 16] (SVC: AAL_Frontal_Superior_Medial_Left, p=0.004), anterior cingulate cortex (ACC) at [15, 33, 30] (SVC: AAL_Cinculum_Ant_Right, p=0.024), and in medial BA25 region (SVC: BA25 binary mask generated from WFU Pickatlas toolbox, p=0.045) (see Figure 5.3(a), 5.3(b), 5.3(c)). No significant correlation was observed between the accuracy for low-mentalizing videos and any GM volume in the medial line of the PFC region. A significant positive correlation was revealed between the accuracy for dyad videos and the GM volume in multiple PFC sub-regions along the medial line, including BA25 region at [12, 30, -15] (SVC: BA25 binary mask generated from WFU_Pickatlas toolbox, p=0.036) (see Figure 5.3(d), as well as BA9 and BA11 regions using a lenient threshold at p<0.001). In addition, the accuracy for group videos was found to positively correlate with the GM volume in the dorsomedial PFC region at [-5, 51, 15] (SVC: AAL_Frontal_Superior_Medial_Left, p=0.023) (see Figure 5.3(e)).

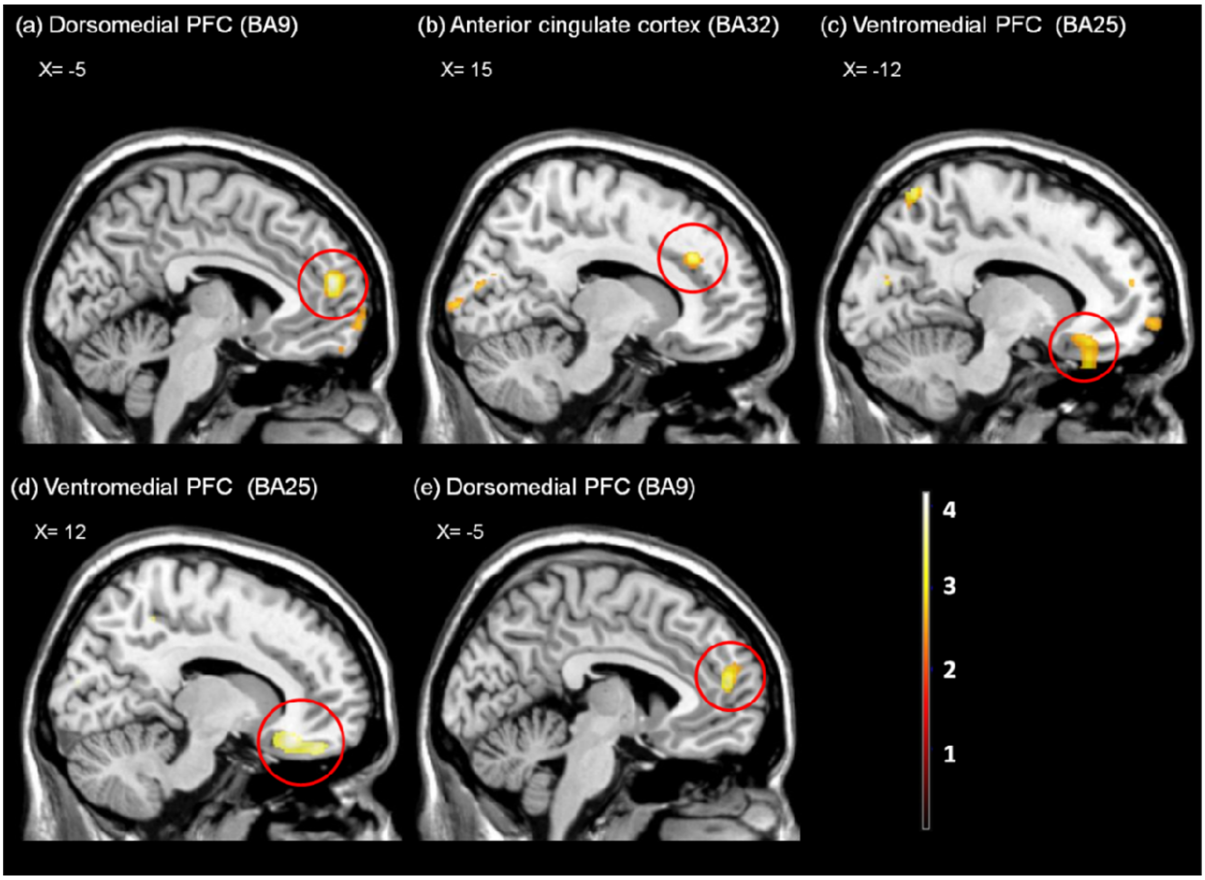


Figure 5.3. The GM volume that significantly correlated with the variables in the video mentalizing test. Accuracy for the high-mentalizing videos was positively correlated with a GM cluster located in the dorsomedial PFC region (panel a), a GM cluster in the anterior cingulate cortex (ACC; see panel b), and a GM cluster in the medial BA25 region (panel c). Accuracy for the dyad conversation videos was positively correlated with a GM cluster in medial BA25 region (panel d). Accuracy for the group conversation videos was positively correlated with a GM cluster in the dorsomedial PFC region (panel e).

Appropriateness

No significant correlations were found between appropriateness score in all conditions and any GM volume in the medial line of the PFC region.

5.7 Discussion of the VBM results in the TD sub-group

The behavioural part of the analysis found similar results to the baseline performance established by the TD group. Repeated measures ANOVA of accuracy and appropriateness did not find a significant effect of intentionality, which indicates that the performance to videos varying in intentionality was comparable either in an absolute or in a continuous way. Correlation analysis of the between-variable effect also demonstrated a consistent pattern of relationship, where positive correlations were observed between accuracy and appropriateness for all videos. This suggests that, behaviourally, the ways of measuring ToM competence using an absolute accuracy and a continuous appropriateness were strongly associated with each other.

The VBM part of the analysis was conducted in two stages. In the first stage, we focused on investigating the function-structure relationship between the PFC region and the behavioural performance for each of the four kinds of videos. In the second stage, we examined the function-structure relationship between the PFC region and the behavioural performance on the main effect of intentionality and complexity separately. VBM regression analysis revealed a positive significant relationship between accuracy for HD videos and the GM volume in several cortical structures along the medial line including medial OFC (BA11), dorsomedial PFC (BA10 and BA8) regions. A recent lesion study conducted by Jenkins et al. (2014) recruited patients with lesions in different PFC sub-regions and found that isolated orbital or medial PFC lesions alone were not sufficient to produce impairments in an emotion recognition test (Montagne, Kesseks, De Haan, & Perrett, 2007) and perspective-taking test (Hynes et al., 2006). The results suggested that it was the combination of lesions in two PFC sub-regions had profound effects on social cognition. It is therefore possible that the identified wide spread function-structure relationship along the midline structure reflected a concept of a network that supported social cognition. The analysis also found a positive significant relationship between accuracy for LG videos and the GM volume in dorsomedial PFC region including BA9, BA8 regions. These identified neural correlates have been consistently found in functional neuroimaging studies that measured ToM competence (see Amodio & Frith, 2006, for review). Nevertheless, it was the accuracy for LG accuracy that was associated with the GM structure in the dorsomedial PFC region. As discussed when considering the baseline performance established by the TD group, the complexity of videos had a profound effect on the engagement of ToM ability. It is possible that social situations involving conversation between more than two characters elicit equally complex interpersonal communication, regardless of the level of intentionality required. To support this speculation, a positive relationship was also observed between accuracy for HG videos and the GM volume in dorsomedial PFC region using a lenient threshold at $p<0.001$ whole brain uncorrected. This potential link, together with the association between accuracy for LG accuracy, suggests that the ability to make correct social decisions involving group conversation could be related to the regional volume of dorsomedial PFC region, a frequently reported structure in social cognition. On the other hand, VBM regression analysis using appropriateness for all four kinds of videos did not find any significant relationships in any PFC region. Despite the behavioural part of the results revealing strong correlations between accuracy and appropriateness in all conditions, it seems that the function-structure association between ToM competence and the medial PFC region could be only observed when measuring ToM competence in an all-or-none way. It may be, in psychometric terms, which for this test at least, “a miss is as good as a mile”.

In the second stage of the VBM analysis, we examined the neural correlates that associated with the main effect of intentionality and complexity separately. VBM regression analysis revealed a positive significant correlation between accuracy for high-mentalizing videos, but not for low-mentalizing videos, and the GM volume in multiple midline structures including the dorsomedial PFC region, the anterior cingulate gyrus, and BA25 region. This observed function-structure relationship corresponded well with previous fMRI studies demonstrating dorsomedial PFC activations in tests involving ToM abilities compared with the control conditions (Gallagher et al., 2002; Castelli et al., 2000; Hynes et al., 2006). Furthermore, the anterior cingulate gyrus was shown to be one of the regions of the social brain (Blakemore, 2008) that was involved with social cognitive processes. This was in line with the findings reported by Jenkins et al. (2014), where social cognition was supported by a combination of the functional role from different cortical regions instead of solely relying on one core structure. On the other hand, VBM regression analysis on the main effect of complexity found significant relationships between accuracy for dyad videos and the GM volume in BA25 region. This observed GM structure located closely to the medial OFC activation (peak MNI: 0, 36, -21) in the ‘influence model’ reported by Hampton et al. (2008). In the influence model, an interactive strategy involving tracking other player’s actions, as well as incorporating inspection of how other’s action would influence back to self was simulated. It is therefore possible that this BA25 structure including the medial OFC region supports social interaction that emphasises one-on-one perspective-taking processes. In comparison, accuracy for group videos was found to positively correlate with the GM volume in the dorsomedial PFC region. This finding supported our speculation that the dorsomedial PFC region is associated with deciphering social situations involving larger amounts of social information (e.g., conversation involved more than two characters), but not with social situations involving a smaller scale of interaction, like conversation between only two characters. Taken together, this distinct link between accuracy for dyad and group videos and the PFC sub-regions along a dorsal-ventral axis may highlight a differentiation in a social cognition network, where the dorsal part of the medial PFC region is involved with processing more complex situations, and the ventral part of the medial PFC region is involved with processing less complex situations.

5.8 Atypical performance of mentalizing ability in ASD subjects

Ever since the study of Baron-Cohen, Leslie, & Frith (1985) reported that children with ASD lack of theory of mind, ASD research has focused on the nature and the cause of this deficit on interpersonal communication. In Baron-Cohen et al. (1985), the ‘Sally-Anne’ test showed that children with ASD failed this test by assessing false belief compared with typical-developing children. It was then proposed that the impairment in ToM could be indexed by failure on false belief tests, and was viewed as the cause of the deficits on social interaction in ASD individuals. Several psychological tests purportedly measuring mentalizing ability found converging results showing children and adults with ASD had relatively poor performances than the control subjects. For example, the ‘Strange Stories test’ presented mental and control stories targeting at understanding non-literal interpersonal conversations like bluffs, jokes, sarcasm, white lies, etc. (Frith and Happe, 1994; White, Hill, Happe, & Frith, 2009). Other ToM tests implemented visual stimuli to depict human or human-like interactions in order to generate complex social situations that require ToM-related ability. Baron-Cohen et al. (1997) developed a ‘Reading the Mind in the Eyes’ test that required subjects to ‘read’ a person’s mental state based on the information around the presented eyes stimuli (see also Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Other ToM tests involved stimuli movements like Castelli et al. (2002), who recruited ASD adults and asked them to watch animations of two triangles moving randomly, goal-directly, or with implied interactions. Paradigms using more realistic experimental stimuli with actual humans measuring ToM capability like the Awkward Moment test (Heavey et al., 2000), which used commercials that combined both visual and auditory inputs to show interpersonal interactions. Other tests like the ‘Reading the Mind in Films’ test (Golan et al., 2006) and the ‘Movie for the Assessment of Social Cognition’ (MASC; Dziobek et al., 2006), which used videos that showed more realistic scenarios to illustrate daily social interactions between people. Despite the difference in experimental stimuli and paradigms, all of these ToM tests aimed to assess the ability to understand other’s mental states, and found that ASD subjects had impaired performance compared with control subjects. It is therefore plausible to suspect that ToM-related dysfunction is a core symptom of ASD, but the causes or the potential contributions of this impaired ToM ability in ASD is still unclear.

Previous theories implicate several possible causes for the observed ToM-related deficits in ASD. Baron-Cohen et al. (1985) proposed a defective meta-representation as the cause of impaired ToM. Further models investigating this meta-representation deficit defined it as a cognitive development mechanism that enabled TD children to represent ToM module in their own mind, and further used this meta-representation to reason about the behaviours of others (Leslie, 1987; Leslie and Roth, 1993). Similar accounts proposed that the concept of 'self' is deeply embedded in the social world and is integrated with many social behaviours, and this integral relationship between the self and the social world is referred as simulation theory (e.g. Goldman, 2006). Evidence was received from studies investigating infants (Meltzoff and Brooks, 2008), children and adults (Birch and Bloom, 2003; 2004), and the neural network including the medial part of the PFC region was also identified (Gallese, 2007; Lombardo et al., 2010). Other possible explanations including problems with language comprehension in order to make pragmatic inferences (see Loukusa and Moilanen, 2009), emotional recognition to understand more complex perception of faces (Castelli, 2005), and the potential indirect influence from executive dysfunction (see Hill, 2004; Robinson, Goddard, Dritschel, Wisley, & Howlin, 2009) were also proposed. In the video mentalizing test developed for the present study, we used short video clips as stimuli and this has several advantages for investigating the explanations for ToM deficits amongst ASD individuals. In order to have good ecological validity, the videos included representations of the characters' mental states by showing perceptual, conative, emotional or epistemic features. Therefore, each of the 15-second videos actually contained abundant social information, including language comprehension, emotion recognition to process. In the testing phase, a constant neutral question was raised and the options were formatted in MCQs varying in appropriateness. Therefore, subjects could form a stable representation to respond to this relatively stable format of questions, and focused on answering the questions from their own perspective (e.g., the question was always 'Which of these statements best describes the situation you have just seen?')

In order to examine the ToM-related deficits amongst ASD subjects using the video mentalizing test, several speculations were first proposed based on the baseline behavioural performance established by the 103 TD subjects and the identified neural correlates from the 62 TD subjects from the TD sub-group. Compared with previous ToM tests using video as stimuli, the overall accuracy from the baseline behavioural result established by 103 healthy TD subjects indicated that the mentalizing demands of the test were quite high in the current paradigm (mean accuracy=0.73), compared with 0.75 in the Awkward Moment test (Heavey et al., 2000), 0.85 in the ‘Reading the Mind in Films’ test (Golan et al., 2006) and 0.76 in the MASC (Dziobek et al., 2006). VBM regression analysis revealed that accuracy for high-mentalizing videos were associated with the GM volume along the midline structure including dorsomedial PFC, anterior cingulate cortex, and medial OFC regions, but no relationship was found between accuracy for low-mentalizing videos and any PFC regions. This suggested that the ability to correctly answer videos involving a higher level of intentionality was positively correlated with the size of cortical areas in a ToM network (Frith and Frith, 2003). As a result, based on the previous findings demonstrated in ToM tests, we hypothesised that the ASD subjects would show selective impairments to videos required high intentionality (high-mentalizing videos), situations that involved making inferences to the character’s mind, but not to videos requiring only a low level of intentionality (low-mentalizing videos), which did not involve making inferences to the character’s mental states. On the other hand, as discussed in earlier sections, we suspected that videos involving more than two characters contained more social information to process than videos involving only two characters. If the ToM deficits originated from deficits in abilities such as comprehension, visual or emotion recognition, then the ASD subjects would find it more difficult to answer group videos correctly, compared with TD subjects, and subsequently lead to a group x complexity interaction showing more drastic impairments to group videos. Furthermore, the questions we used in the video mentalizing test were multiple choices varying in appropriateness. Previous ToM tests measuring a group difference mainly focused on the absolute accuracy, where the performance could only be scored as either correct or incorrect. It is possible that ToM competence between individuals could be measured in a continuous way, where the deficits identified amongst ASD individuals would no longer be significant when calculated in a continuous way. For example, the previously labelled ‘incorrect’ response could be merely ‘less appropriate’ than the correct answer, or the ‘most appropriate’ one, and thus intensified the observed impairment on social communication in ASD using an arbitrary way. As a result, we further explored if mentalizing deficits in ASD were still valid using appropriateness as the index for ToM competence.

5.9 Behavioural result between the ASD and the TD groups

The accuracy, appropriateness and reaction time for each condition were entered into repeated measures ANOVA with intentionality, complexity as within-subject factors, and group as between-subject factors. In this section, we focused on examining the main effect and the interaction of group. The behavioural result of each group including accuracy, appropriateness, and reaction time in each condition are summarised in Table 5.5.

Table 5.5. Accuracy, appropriateness, and reaction time (msec.) between conditions in the video mentalizing test of the TD and the ASD groups. Panel (a): the result in each condition; panel (b): the main effect of intentionality and complexity.

(a)	TD		ASD	
	mean	SD	mean	SD
Accuracy				
HD videos	0.77	0.16	0.67	0.19
HG videos	0.70	0.20	0.58	0.24
LD videos	0.85	0.16	0.78	0.19
LG videos	0.60	0.22	0.58	0.20
Appropriateness				
HD videos	3.62	0.36	3.42	0.54
HG videos	3.40	0.47	3.09	0.66
LD videos	3.71	0.34	3.52	0.42
LG videos	3.27	0.45	3.25	0.36
Reaction time (msec.)				
HD videos	10730.7	2933.6	11920.4	3564.5
HG videos	13297.1	3077.4	15050.4	4151.8
LD videos	10549.0	2751.2	11246.3	3648.6
LG videos	11588.6	2487.7	11709.3	3294.5

(b)	TD		ASD	
	mean	SD	mean	SD
Accuracy				
High-mentalizing	0.74	0.13	0.63	0.17
Low-mentalizing	0.72	0.15	0.68	0.16
Dyad conversation	0.81	0.12	0.73	0.14
Group conversation	0.65	0.17	0.58	0.16
Appropriateness				
High-mentalizing	3.51	0.32	3.26	0.46
Low-mentalizing	3.49	0.32	3.39	0.31
Dyad conversation	3.66	0.28	3.47	0.35
Group conversation	3.34	0.37	3.17	0.38
Reaction time (msec.)				
High-mentalizing	12013.9	2749.8	13485.4	3537.5
Low-mentalizing	11068.8	2478.0	11477.8	3322.6
Dyad conversation	10639.9	2704.6	11583.3	3474.0
Group conversation	12442.8	2591.7	13379.8	3430.3

Accuracy

Repeated measures ANOVA found a significant main effect of group ($F(1,131)=8.788$, $p=0.004$), which showed that the ASD group had lower accuracy for all kinds of videos than the TD group in general. The analysis also revealed a significant main effect of complexity ($F(1,131)=81.759$, $p<0.001$), where accuracy was significantly higher for dyad videos than for group videos. No significant main effect of intentionality was found ($F(1,131)=1.459$, $p=0.229$). The three-way interaction between group, intentionality, and complexity was not significant ($F(1,131)=0.955$, $p=0.330$), but a marginally significant interaction between group and intentionality ($F(1,131)=3.679$, $p=0.057$) was found (see Figure 5.4). The deficit when comparing ASD subjects with TD subjects was much higher for high-mentalizing videos than for low-mentalizing videos. No significant group x complexity interaction was found ($F(1,131)=0.301$, $p=0.584$). A significant intentionality x complexity interaction was found ($F(1,131)=16.843$, $p<0.001$), which showed that both groups had higher complexity effect in low-mentalizing videos than in high-mentalizing videos.

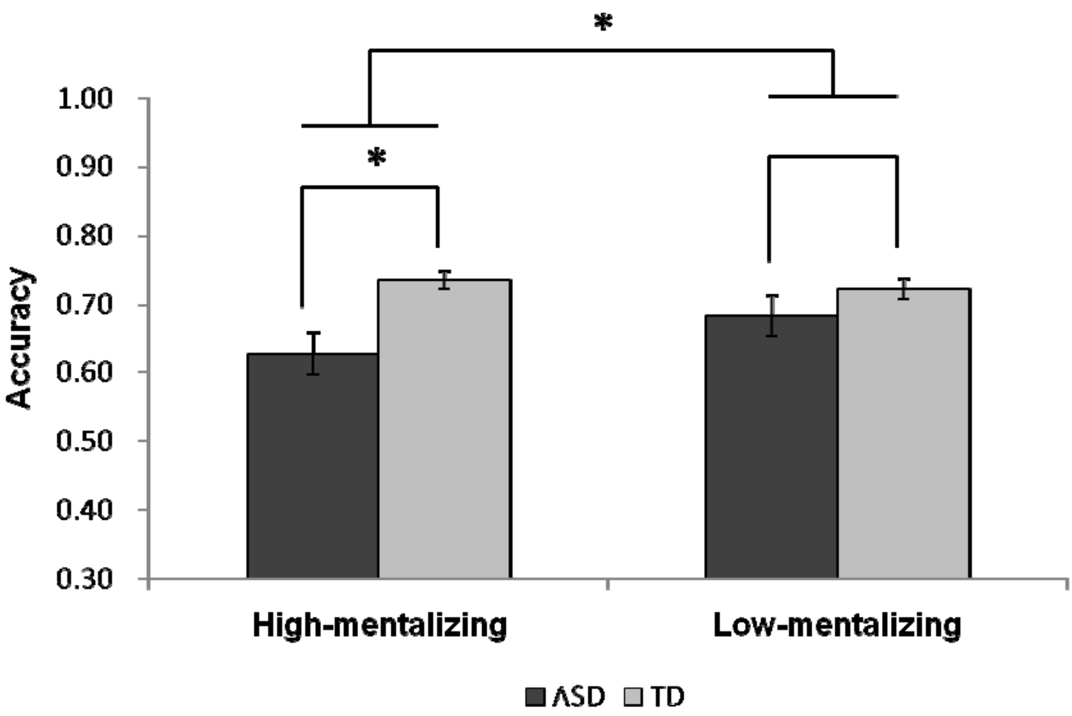


Figure 5.4. The group x intentionality interaction on the accuracy in the video mentalizing test.

Appropriateness

Repeated measures ANOVA showed a significant main effect of group (F(1,131)=9.486, p=0.003), where appropriateness was significantly lower in the ASD group than the TD group. The analysis also found a significant main effect of complexity (F(1,131)=66.103, p<0.001), which showed that all subjects responded to dyad videos more appropriately than to group videos. No significant main effect of intentionality was found (F(1,131)=1.931, p=0.167). The three-way interaction between group, intentionality, and complexity was not significant (F(1,131)=2.753, p=0.099). No significant interaction between group x intentionality (F(1,131)=3.607, p=0.06), group x complexity (F(1,131)=0.141, p=0.707), and intentionality x complexity F(1,131)=1.068, p=0.303) were found.

Reaction time

Repeated measures ANOVA did not find a significant main effect of group (F(1,131)=2.777, p=0.098). The analysis identified a significant main effect of intentionality (F(1,131)=92.876, p<0.001), which showed that the response speed was significantly longer for high-mentalizing videos than for low-mentalizing videos. The analysis also found a significant main effect of complexity (F(1,131)=106.770, p<0.001), where all subjects responded significantly slower to group videos than to dyad videos. Repeated measures ANOVA did not find a significant three-way interaction between group, intentionality, and complexity (F(1,131)=3.462, p=0.065). Importantly, a significant group x intentionality interaction was identified (F(1,131)=12.027, p=0.001), and the interaction was confirmed by a significant response slowness (ASD vs. TD) in high-mentalizing videos (t(131)=2.410, p=0.017), but this slowness was not significant in low-mentalizing videos (t(131)=0.733, p=0.465). The response slowness in ASD subjects, compared with TD subjects, was more prominent for high-mentalizing videos than for low-mentalizing videos (see Figure 5.5). A significant intentionality x complexity interaction was found (F(1,131)=46.844, p<0.001), where the intentionality effect was higher for group videos than for dyad videos. No significant group x character interaction was found (F(1,131)=0.000, p=0.985).

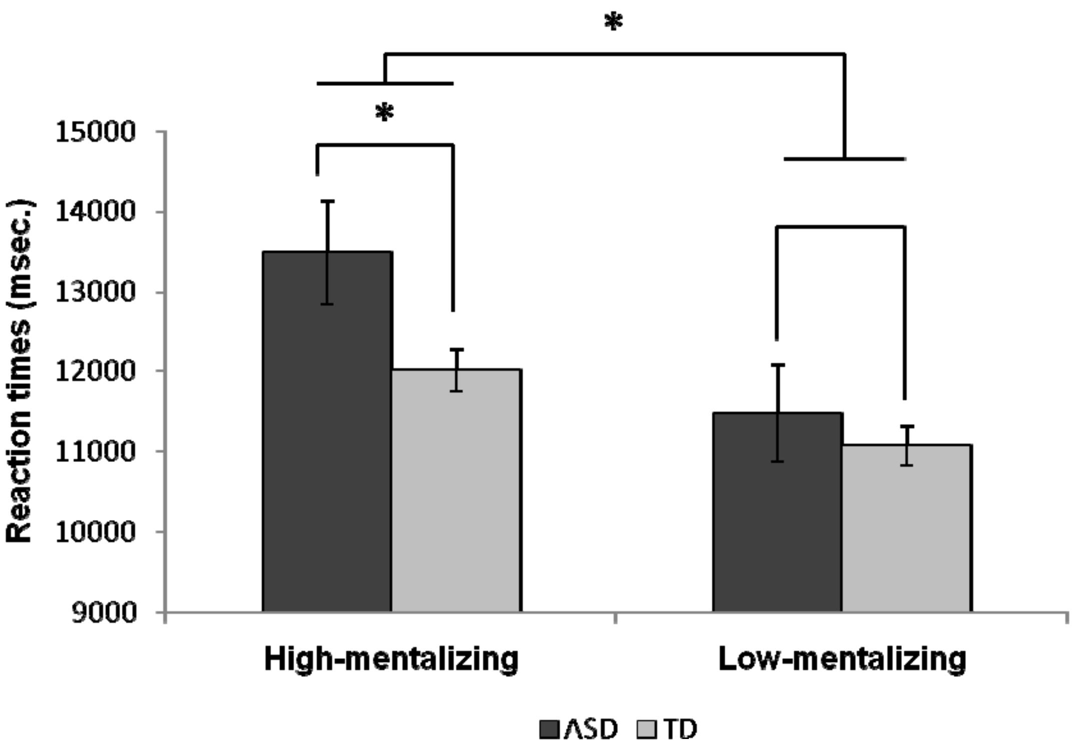


Figure 5.5. The group x intentionality interaction on the reaction time in the video mentalizing test.

5.10 Discussion of the behavioural result between the ASD and the TD groups

The video mentalizing test used videos depicting daily interpersonal communications with varying level of intentionality and complexity. The analysis of this section focused on the between-group effect on accuracy, appropriateness score, and reaction times for HD, HG, LD, and LG videos. Repeated measures ANOVA on accuracy identified a significant main effect of group, which suggested that ASD subjects found it more difficult to choose the correct option when passively watching videos involving daily conversation between other people, regardless of the intentionality and the complexity of the scenarios. Importantly, a marginally significant group x intentionality interaction was found, which revealed that ASD subjects had selectively lower performance on high-mentalizing videos compared with low-mentalizing videos. This was consistent with a vast literature investigating Tom-related deficits amongst ASD subjects using various kinds of ToM tests (Happe, 1994; Baron-Cohen et al., 1997; Castelli et al., 2002; Heavey et al., 2000; Golan et al., 2006; Dziobek et al., 2006). A possible explanation that accounts for the deficits in processing social situations involved mentalizing pinpointed the impairments originating from fundamental stages, for example, processing human faces, as a crucial aspect for the video mentalizing test. Studies have consistently found an atypical functional role of the visual processing system in ASD individuals, which includes evidence showing abnormal activations in fusiform face area, under-connectivity with the frontal regions, atypical visual scanning of faces, and unique strategies for face processing (Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Pelphrey, Sasson, Reznick, Paul, Goldman, & Piven, 2002; Hubl et al., 2003; Darkin and Frith, 2005; Behrmann, Thomas, & Humphreys, 2006; Koshino, Kana, Keller, Cherkassy, Minshew, & Just, 2008; Muller, Shih, Keehn, Deyoe, Leyden, & Shukla, 2011). These abnormal bottom-up mechanisms might cause ASD individuals to be unable to process fast-pace, dynamic sequences of facial expressions that include social information crucial for mentalizing. On the other hand, repeated measures ANOVA did not find a significant group x complexity interaction, and a significant main effect of complexity suggested that the ASD subjects also had more difficulty processing group videos than processing dyad videos, similar as TD subjects. This significant main effect of complexity revealed a profound effect on the number of characters involved in conversation using video stimuli, and further suggests a possible direction in controlling for the 'qualitative' difference of the experimental stimuli used for ToM paradigms.

Repeated measures ANOVA of appropriateness also identified a significant effect of group, where the ASD group responded less appropriately than the TD group for all kinds of videos. This was consistent with the finding using accuracy to measure mentalizing ability. The analysis of appropriateness revealed a tendency for a group x intentionality interaction, which was similar to the pattern demonstrated in accuracy. Furthermore, comparable effects were also identified, which included a significant main effect of complexity and null group x complexity interaction when using appropriateness. Together these results indicated that, behaviourally, measurement for ToM competence using an absolute accuracy and a continuous appropriateness yielded similar results when comparing ASD subjects with TD subjects.

Repeated measures ANOVA of reaction time did not find a significant main effect of group, which suggests that the response speed in ASD subjects was comparable with the baseline performance established in TD subjects. This null effect indicated that, despite ASD subjects responding less accurately and less appropriately in general, they did not respond significantly slower for processing the all the video clips in general in the current paradigm. Nevertheless, a significant 2 x 2 interaction between group x intentionality was found, which demonstrated that the ASD group responded significantly slower in high-mentalizing videos than the TD group, but this slowness was not evident in low-mentalizing videos. This selective slowness on processing videos that required higher level of intentionality was in line with the pattern identified on accuracy, and highlighted a selective deficit to high-mentalizing videos accompanied with lower performance and slower responding in ASD subjects, whilst demonstrating comparable performance to the 'baseline' low-mentalizing videos compared with TD subjects. No significant group x complexity interaction was found, which indicated that, despite significant a main effect of complexity, the number of characters involved in the conversation affected the performance of both groups in a similar way. These null interactions between group and complexity suggested that the complexity factor was not a powerful variable to distinguish ASD subjects from TD subjects, and as a result, we focused on the main effect of intentionality for further analyses conducted in later chapters discussing the between-test effect.

Chapter 6. PFC battery – the cartoon faux pas test

6.1 Measurements for detection to social norm violation

In order to measure ‘Theory of Mind’ (ToM) competence, various psychometric tests have been designed to test the ability to make correct inferences of other’s mental states. A situation where “a speaker says something without considering if it is something that the listener might not want to hear or know, and which typically has negative consequences that the speaker never intended” is referred as a ‘faux pas’ (Baron-Cohen et al, 1999). The capability to successfully recognise of this violation to social norm is viewed as an advanced application of ToM, and is closely related to detection of embarrassment. It has been shown that adults with medial PFC lesions under-detect faux pas (Stone et al., 1998; Lee et al., 2010), which indicates that the PFC region played an important role to recognise a faux pas, or to detect a violation to social norm.

The original faux pas test (Baron-Cohen et al., 1999) presented social situations using audio stories with neutral tones recorded on tapes as experimental stimuli. The purpose of using audio stories was to control for the effect from the visually presented facial expression, and to avoid the potential contribution of emotional turbulence hidden with tone changes. Nevertheless, in real-life interactions, the change of audio tone often contained subtle social cues, and was essential for successful faux pas detection. As a result, the use of audio recordings without naturalistic changes of tones may lack ecological validity. Another important issue regarding faux pas tests is the way of scoring. In the experiment 3 of Baron-Cohen et al. (1999), ten control questions without faux pas were included and intermixed with ten faux pas stories. However, no direct measurement of the accuracy for correctly rejecting stories without faux pas was calculated. Similarly, Zalla, Sav, Stopin, Ahade, and Leboyer (2009) used a modified version of the faux pas test including ten control questions without any faux pas that were mixed with ten faux pas stories, and the scores for faux pas and control stories were calculated separately. Subjects could only acquire scores if correct rejections were made to the control stories having no faux pas. Importantly, in previous faux pas tests (Baron-Cohen et al., 1999; Zalla et al., 2009), the testing phase consisted of multiple questions asking about different aspects of faux pas, including detection, identification, and false belief. The results highlighted that successful faux pas responses involved different cognitive components. The multiple processes while answering faux pas questions indicates that complex underlying cognitions like social reasoning and/or emotional appreciations are required for recognising social embarrassment. Despite the role that different sub-components play while identifying a faux pas, to realise that an embarrassing situation has happened can be a sudden awareness, without step-by-step reasoning in real life. It is possible that the process of detecting a faux pas can be determined by one's criterion to social violations. Signal detection theory (SDT) delineates a decision making process that is used to distinguish signal from noises (see Nevin, 1969, for review; Harvey, Hammond, Lusk, & Mross, 1992, for application). When a signal is present, based on subject's yes no responses, outcomes are referred to as hit (yes) and miss (no) respectively. On the other hand, if a signal is absent, based on subject's yes or no responses, the outcomes are referred as false alarm (yes) and correct rejection (no) respectively. In the following faux pas paradigm, successful faux pas detection is referred to a combined ability to detect a faux pas when there is one, and to reject a non-faux pas when there is not one. Furthermore, we used faux pas related questions distinct from comprehension questions in order to control form differences in reading, comprehension, or IQ abilities. This enabled us to have clear measurements of an individual's ability in detecting a faux pas.

In order to investigate the ability for faux pas detection using a signal detection approach, we designed a cartoon faux pas test, which used cartoons to depict social interactions amongst characters. The questions in the cartoon faux pas test were either asking subjects if there was anything embarrassing for faux pas related cartoons, or asking subjects difficult questions with no faux-pas or social cognition content for comprehension cartoons. In the faux pas related cartoons, half of the cartoons contained a faux pas (faux pas condition) and the other half did not (non-faux pas condition). Subjects were required to determine if there was any social norm violation. Following signal detection theory, the accuracy for the faux pas condition was referred as 'hit', and the accuracy for the non-faux pas condition was referred as 'correct rejection'. Given that the question asked in the faux pas related cartoons were always 'Embarrassing?', there was a potential confound, as mentioned in the video mentalizing test chapter, that subjects might got intrigued by the question and gave more 'yes' responses than to give 'no' responses. As a result, we hypothesised that accuracy in the faux pas condition would be higher than in the non-faux pas condition.

6.2 Methods of the cartoon faux pas test

Materials and Design

The cartoon faux pas test used 52 cartoon stories using two or three frames to visually illustrate social interactions. Each cartoon story was originally hand-drawn (by Flora Thiebaut, a UCL MSc Cognitive Neuroscience student), scanned and transformed into digital version by using the Comic Live software (http://plasq.com/products/comiclife2). The facial parts of the characters were deliberately left blank to control for the emotional contribution and the conversations between characters were presented in speech bubbles. The 52 cartoon stories consisted of three conditions: 18 cartoon stories with faux pas, 18 cartoon stories without faux pas and 16 stories asking the comprehensive aspect of the stories. In the stories containing a faux pas, the appearance of the dialogue that caused embarrassment was counterbalanced, where half of the embarrassment happened in the second frame and the other half happened in the third frame. Importantly, in order to investigate faux pas detection using signal detection approach, the same question ('Embarrassing?') was presented in both the faux pas and non-faux pas conditions. Subjects were asked to respond by pressing either the left arrow or the right arrow key to indicate "yes" or "no" to the question. The comprehension condition depicting stories without any faux pas served as a baseline condition to see if subjects understand the cartoon stories properly. The questions asked in the comprehension condition were different from each other and only focused on the comprehension aspect of the stories.

<u>Procedure</u>

The cartoon faux pas test was presented on a laptop using E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA). Subjects were asked to sit approximately 80 centimetres from the screen in a quiet testing room. Subjects were instructed to respond as quickly as possible with a good balance of speed and accuracy. At the beginning of the test, instructions with two of the comprehension cartoons were used for practice in order to let the subjects familiarize with the layout of the stories (see Figure 6.1). Seven comprehension cartoons were presented first, and then the faux pas stories were introduced along with two practice stories, one story with a faux pas (see Figure 6.2) and the other story without a faux pas (see Figure 6.3). The remaining 34 faux pas and non-faux pas cartoons were then presented to the subjects. Lastly, seven more comprehension cartoons were presented. The order of the cartoons was counter-balanced for order using a Latin-square design and was held constant across subjects. A maximum threshold for reaction time was set at 32 seconds based on the pilot data. To ensure subjects were ready for each story, a confirmation saying: “Are you ready? Press the spacebar and the cartoon will appear.” was presented before the display of each story. The proportion of correct YES/NO answers was balanced to avoid a fixated response tendency. The cartoon faux pas test took each subject around 15 minutes to complete.

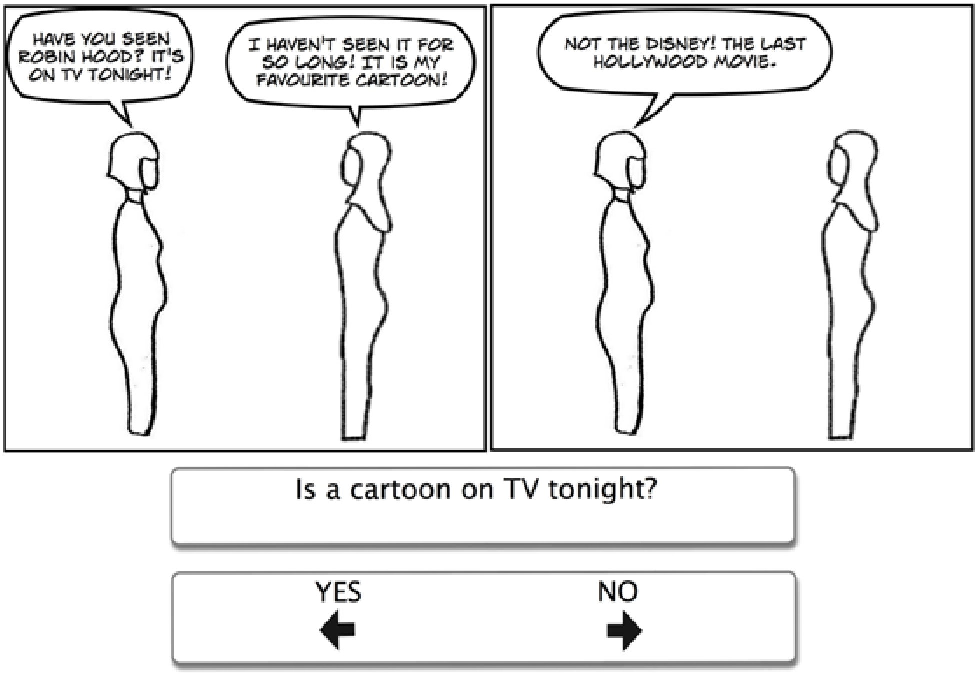


Figure 6.1. An example of the comprehension cartoons. The comprehension cartoons did not contain any faux pas component, and the questions asked differed between each other.

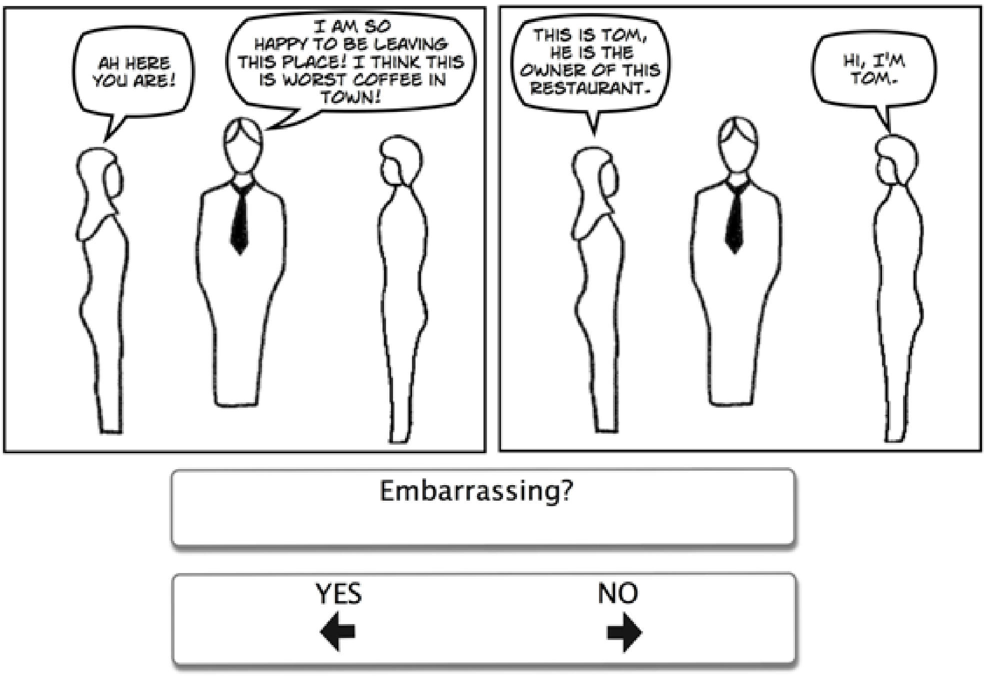


Figure 6.2. An example of the faux pas cartoons. In the depicted story, the male character waering a tie committed a faux pas that made other characters felt embarrassing, and the questions asked were always ‘Embarrassing?’.

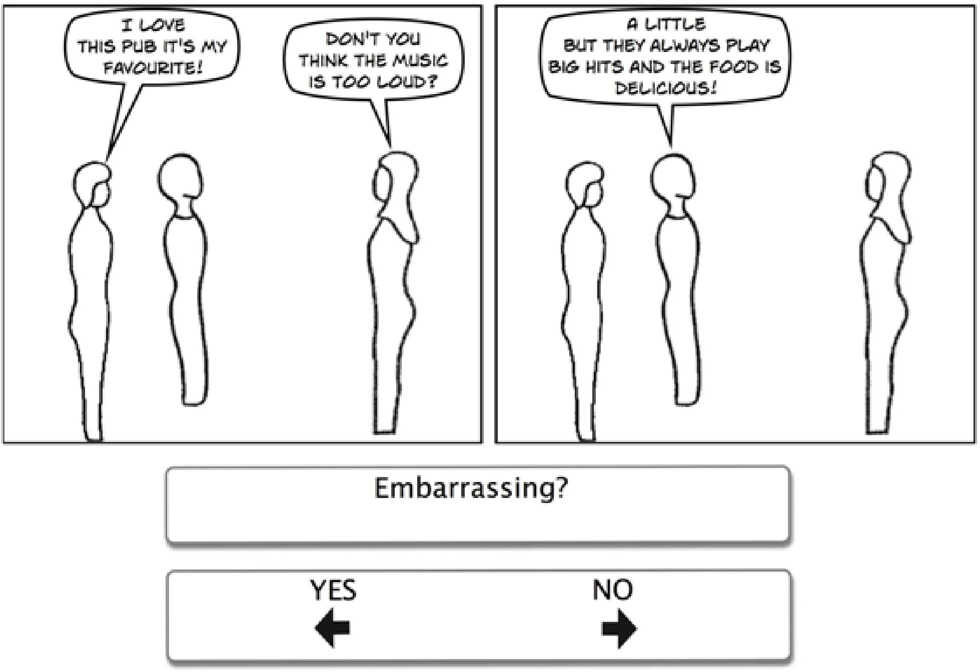


Figure 6.3. An example of the non-faux pas cartoons. In the depicted story, no faux pas was committed by any of the characters, but the questions were always ‘Embarrassing?.

6.3 Behavioural result of the TD group

Accuracy

The behavioural results of the TD group were summarised in Table 6.1. The accuracy and the reaction times were entered into repeated measures ANOVA with condition (faux pas, non-faux pas, and comprehension) as a within-subject factor. The behavioural results of the cartoon faux pas test in the TD group were summarised in Table.6.2. Repeated measures ANOVA on accuracy first revealed that the assumption of sphericity had been violated (χ^2 (2)=12.937, p=0.002 in

Mauchly's test), and degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (ε=0.908). The result showed a significant effect of condition ($F(1.82,185.13)=6.015$, $p=0.004$, and post-hoc test using Bonferroni correction identified that the accuracy for the non-faux pas cartoons was significantly higher than the faux pas cartoons ($p=0.014$) and the comprehension cartoons ($p=0.031$). No significant difference on accuracy was found between the faux pas and the comprehension cartoons.

Reaction time

Repeated measures ANOVA on reaction time first confirmed that the sphericity assumption has been met (χ^2 (2)=5.133, $p=0.077$ in Mauchly's test). The result found a significant effect of condition ($F(2,204)=8.679$, $p<0.001$), and post-hoc test using Bonferroni correction demonstrated that the reaction time in the faux pas condition was significantly longer than in the non-faux pas condition ($p<0.001$) and in the comprehension condition ($p=0.004$). No significant difference on reaction times was found between the non-faux pas and the comprehension conditions.

Table 6.1. Accuacy and reaction time between conditions in the cartoon faux pas test of the TD group.

		mean	SD
Accuracy			
	Comprehension	0.81	0.12
	Faux pas	0.80	0.12
	Non-faux pas	0.86	0.15
Reaction time (msec.)			
	Comprehension	9027.2	2928.5
	Faux pas	9509.3	2913.7
	Non-faux pas	9007.8	2941.5

Correlation analysis

Due to all the variables deviated from normal distribution (p value below 0.05 in Kolmogorov-Smirnov Test), Spearman's rank-order correlation analysis was conducted in two different approaches. In the first approach, we focused on the within-variable effect, where the relationships on accuracy between the three experimental conditions (faux pas, non-faux pas, and comprehension) and reaction time between the three experimental conditions were examined. In the second approach, we then analysed the between-variable effect, where the relationships between the three experimental conditions using accuracy and reaction time were examined separately.

In the first approach, correlation analysis revealed that the accuracy for the faux pas cartoons was significantly correlated with the accuracy for the comprehension cartoons (r_s (103)=0.276, p=0.005). A significant negative correlation was found between the accuracy for the non-faux pas cartoons and the accuracy for the faux pas cartoons (r_s (103)=-0.202, p=0.04), but no significant correlation was found between the accuracy for the non-faux pas cartoons and the accuracy for the comprehension condition (r_s (103)=0.067, p=0.501). Analysis on the reaction times showed significant correlations between all pair-wise comparisons between the three types of cartoon (all p<0.001). In the second approach, significant relationships were found between the accuracy and the reaction times for the faux pas cartoons (r_s (103)=0.227, p=0.021). No significant relationships were found between the accuracy and the reaction times for the non-faux pas cartoons (r_s (103)=0.134, p=0.178) and for the comprehension cartoons (r_s (103)=-0.001, p=0.992).

6.4 Discussion of the behavioural result in the TD group

The cartoon faux pas test used cartoons to illustrate social interactions and focused on measuring the ability for faux pas detection. The comprehension aspect of the test was isolated, which allowed measuring the accuracy for ‘hit’ and ‘correct rejection’ in faux pas detection using signal detection approach. The results on accuracy contradicted our hypothesis and revealed that the accuracy was significantly higher in the non-faux pas condition than in the faux pas condition. Furthermore, the accuracy in the non-faux pas condition was significantly higher than the ‘baseline’ comprehension condition, but no significant difference was found between the faux pas and the comprehension condition. From the perspective of signal detection, better detection in the non-faux pas condition (correct rejection) could be viewed as the implementation of a certain strategy, or a rightward shift of the response criterion. This was associated with a higher propensity to give *no* responses when facing potential social embarrassment. Analysis on reaction time showed that subjects responded significantly slower in the faux pas condition than in the other two conditions. This suggested a selective ‘cost’ on response speed during decisional process to social situation actually contained a faux pas component, but demonstrated comparable response speed to situation did not contain any faux pas component with the ‘baseline’ comprehension scenarios. As a result, the behavioural performance of the TD group revealed that better accuracy and faster responses on ‘correct rejection’ than on ‘hit’ to detect potential social norm violations. In signal detection theory, the general tendency to give more *yes* or *no* responses reflected a concept of ‘response bias’, as determined by the position of an internal criterion between individuals. In the cartoon faux pas test, it is possible that TD subjects had a general propensity to give more *no* response when evaluating possible social embarrassment. A potential factor that resulted in this rightward shift of criterion might be a relatively higher threshold for social embarrassing detection. For example, Naylor and Lawshe (1958) demonstrated that subjects reported detection of swear words less often than neutral stimuli, which reflected that a ‘false alarm’ was more embarrassing for claiming swear words were detected than for neutral stimuli. This cautious attitude about reporting them led to a higher threshold to give a *yes* response, which subsequently led to more *no* responses in a forced-choice environment. Similar effect was shown in Thomas and Hogue (1976), where jury instructions had a profound effect on the willingness to convict a suspect, e.g., criminal cases with lenient sentences required less evidence to draw a conviction than cases with severe penalties. In the context of the cartoon faux pas test, it was more ‘embarrassing’ to give a ‘false alarm’ than to a ‘miss’ when facing potential social embarrassment. Furthermore, the way of instructions given, or the understanding to ‘embarrassing’ might affect the criterion to give *yes* or *no* responses to potential social rule violation. In the faux pas and the non-faux pas conditions, a question constantly appeared on the screen asking ‘embarrassing?’, and this might intrigue TD subjects to suspect that ‘there supposed to be something embarrassing’. A supporting evidence of the speculation came from the significantly slower reaction time in the faux pas than in the non-faux pas condition.

Spearman’s rank-order correlation found a significant negative relationship between the accuracy for the faux pas and the non-faux pas cartoons, which indicated that the better performance in one condition accompanied with the worse performance in the other. This confirmed the contribution of the location of criterion in faux pas detection using a signal detection approach, where a higher propensity to give, for example, *no* responses, would inevitably brought higher correct rejection rate and lower hit rate in the cartoon faux pas test. In the between-variable approach, a significant positive relationship was only identified between the accuracy and the reaction time for the faux pas cartoons, which could be viewed as a classic psychological effect of speed-accuracy tradeoff (SAT; Fitts, 1954; see Heitz, 2014 for review). The selective lack of SAT for the non-faux pas cartoons indicated that longer consideration did not necessary accompany with better correct rejection rate of a faux pas. This strategic adjustment of SAT in decision-making was modulated by environmental demands (Fitts, 1966), and stochastic accumulators model using computational perspective proposed that responses were produced when the accumulated evidence for one option reached a given threshold, e.g., elevating the threshold led to slower, more accurate responses, and lowering the threshold produced faster yet less accurate responses. It is therefore possible that a shift of internal criterion selectively affected the response bias to decisions upon non-faux pas cartoons, and subsequently resulted in no SAT when requiring rejecting potential non-faux pas situations.

In signal detection theory, the distance between the means of the signal-present and signal-absent distributions was referred as the sensitivity, or d-prime value. The response bias, referred to as the tendency for individuals to decide that a signal is present or is not present, could be dissociated from the sensitivity (see Stanislaw and Todorov, 1999, for discussion). From the perspective of sensitivity, it seems possible that the considered 'strength' of faux pas signals were different from each other in the two conditions (faux pas vs. non-faux pas). From the perspective of response bias, it is possible that subjects had higher tendency to give *no* responses rather than *yes* responses. Both possibilities would lead to a pattern of higher accuracy and faster responding with the non-faux pas cartoons compared to the faux pas cartoons. Further investigation is required to examine the effect of sensitivity and response bias during faux pas detection.

6.5 Neuroimaging findings of detection to social norm violation

In human society, certain conventional behaviours or social rules outline an acceptable social norm during interpersonal communications. In order not to be ostracised, or maintain harmony between group members, it is essential for individuals to meet the social standard that is considered appropriate by others. Under some circumstances, interactions with other people require understanding complex emotional states relying on one's own standards, or originating from concerns about other's understandings of oneself. These emotional states are referred to as ‘self-conscious emotions’, such as the feeling of embarrassment. Recognising such emotional states successfully requires mental abilities including to have a sense of the self, understanding the social norms, and the capability to make inferences about other’s mental states. Previous functional neuroimaging studies have indicated a link between ToM ability and the medial PFC region (Frith & Frith, 2006). Given that the detection of embarrassing situations is comprised of multiple sub-components other than ToM, it seems plausible to suspect that other PFC sub-regions are involved the ability to detect social norm violations. An fMRI study conducted by Berthoz, Armony, Blair, and Dolan (2002) used written stories with different endings including normative behaviours, unintentional violation of social norms or intentional violation of social norms to investigate the neural activities during social norm evaluation. The results showed that both unintentional and intentional violations of social norms activate the medial PFC region, as well as the lateral OFC region. The observed lateral OFC activity suggested that this PFC sub-region not only responded to angry expressions of others (Blair and Cipolotti, 2000; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998) but also responded to actions that may potentially cause others to become angry. This highlights the potential modulatory role that the lateral OFC plays in preventing self and others from engaging in socially inappropriate behaviours. Similarly, activation of the lateral OFC region was also found in other fMRI studies investigating the neural activities involved with processing socially embarrassing conditions. Finger, Marsh, Kamel, Mitchell, and Blair (2006) used written stories with moral transgression (intentional), social transgression (unintentional) or neutral transgression to investigate the brain activations when one ought to modify one’s own behaviours with or without audiences. The results found increased activity in lateral OFC during social transgressions (unintentional) only in the presence of an audience. Similar lateral

OFC activity was also identified in Takahashi et al. (2004) where subjects were required to read short sentences carrying guilt, embarrassment or no emotional content from the first-person perspective and made evaluations as to the level of guilt or embarrassment. The results demonstrated greater activations in the medial PFC, as well as lateral OFC regions, in the embarrassing vs. neutral contrast. These results suggested that lateral OFC activities reflect an evaluation process of social, contextual and emotional information relating to social norm violations.

One of the ways to examine the capability to detect social norm violations is the implementation of a faux pas situation. “Faux pas” refers to social embarrassing situations when social norms are unintentionally violated, and is viewed as an advanced ToM ability. Previous studies using patients with lesions to the PFC region (Stone et al., 1998; Roca et al., 2010; Lee et al., 2010) and people with autism (Baron-Cohen et al., 1999) had shown that the PFC region plays an important role in faux pas detection. Zalla et al. (2009 revealed that people with Asperger syndrome not only performed worse than controls on detecting a faux pas, but also had tendencies to over-detect faux pas situations, where the accuracy was also lower than controls for ‘correct rejection’ to social embarrassment. Furthermore, in Zalla et al. (2009), all subjects were required to answer questions regarding ‘detection’, ‘person identification’, ‘content’, ‘explanation’, ‘the false belief’, and ‘empathy’ to each faux pas story. A similar multi-process manipulation was implemented in Lee et al. (2010), where all subjects were required to answer four questions including ‘detecting a faux pas’, ‘understanding a faux pas’, ‘understanding the recipient’s mental state’, and ‘understanding the speaker’s mental states’. Together these results demonstrated that failure in detecting faux pas may originate from one of the sub-processes and these sub-processes can dissociate from each other.

In the cartoon faux pas test, we used cartoon stories to visually present scenarios involving social interactions. We isolated the comprehension aspect of the test and investigated faux pas detection using a signal detection approach. Given that previous faux pas studies suggested dissociable sub-process during faux pas detection, it is possible that a successful ‘hit’, or a successful ‘correct rejection’ of a faux pas situation relied on different weightings between ToM-related abilities and other processes such as social evaluation of embarrassment. For example, in real-life situations, it seems quite intuitive that when people identify the embarrassed feeling in oneself or others, and as a consequence give a ‘yes’ response, this might require a mental process based on a ToM-related ability. On the other hand, to give a ‘no’ response may require more evaluation of whether social violations were involved, a mental process relied more on social “rule” evaluation. Previous studies have revealed that lateral OFC region is associated with social evaluation (Cunningham, Johnson, Gatenby, Gore, & Babaji, 2003; see Cunningham and Zelazo, 2007 for review). Taken together, we hypothesise that the accuracy for ‘hits’ (relying, in theory, more on ToM ability) would correlate with GM volume in the medial PFC region, whereas the accuracy for ‘correct rejection’ (relying more on social evaluation) would correlated with GM volume in the lateral OFC region. Furthermore, in signal detection theory, the ‘sensitivity’ indicated the degree of overlap between the signal and the noise distributions, and the ‘responses bias’ measured the tendency to give a yes or a no response, as determined by the location of one’s criterion. As a result, we further calculated the value of d prime (d’) as a score for measuring sensitivity, the value of β as a score for measuring response bias, and investigate the neural correlates of this two scores relating to faux pas detection. The formula we used to calculate the values of d’ and β of the cartoon faux pas test were based on Stanislaw & Todorov (1999) using Excel software.

6.6 Behavioural and VBM result in the TD sub-group

Behavioural investigation into the cartoon faux pas test

Accuracy

The behavioural results of the cartoon faux pas test in the TD sub-group were summarised in Table 6.2. Repeated measures ANOVA on accuracy first revealed that the assumption of sphericity had been violated (χ^2 (2)=8.333, p=0.016 in Mauchly's test), and degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (ε=0.910). The result did not find a significant effect of condition (F(1.82,110.99)=2.832, p=0.068.

Reaction time

Repeated measures ANOVA on reaction time first confirmed that the sphericity assumption has been met (χ^2 (2)=3.702, p=0.157 in Mauchly's test). The result found a significant effect of condition (F(2,122)=8.156, p<0.001), and post-hoc test using Bonferroni correction demonstrated that the reaction time in the faux pas condition was significantly longer than in the non-faux pas condition (p=0.002) and in the comprehension condition (p=0.008).

Table 6.2. Accuracy, reaction time (msec.), and the signal detection variables including d-prime, β values in the cartoon faux pas test of the TD sub-group (n=62).

		mean	SD
Accuracy			
	Comprehension	0.84	0.11
	Faux pas	0.81	0.13
	Non-faux pas	0.86	0.15
Reaction time (msec.)			
	Comprehension	9385.7	3128.5
	Faux pas	9943.1	3071.0
	Non-faux pas	9377.3	3179.4
Signal detection variables [a]			
	d-prime	2.31	0.83
	β	3.70	4.25

[a] The formula was provided by Stainslaw and Todorov (1999).

Correlation analysis

All the variables deviated from normal distribution (p value below 0.05 in Kolmogorov-Smirnov Test), and Spearman's rank-order correlation analysis was conducted in the same way as in the TD group. Within-variable Spearman's rank-order correlation analysis revealed that the accuracy for the faux pas condition was significantly correlated with the accuracy for the comprehension condition (r_s (62)=0.299, p=0.018). No significant correlations were found between the accuracy for non-faux pas condition and the accuracy for faux pas condition (r_s (62)=-0.202, p=0.116), nor with the accuracy for non-faux pas condition and the accuracy for the comprehension condition (r_s (62)=-0.018, p=0.889). Analysis on the reaction time showed significant correlations between the three cartoon conditions (p<0.001 in all three pair-wise analyses). Between-variable variable Spearman's rank-order correlation analysis found no significant correlations for all the three kinds of cartoons (all p>0.05).

VBM investigation into the cartoon faux pas test

The VBM part of the result were summarised in Table 6.3. VBM regression analysis first identified a marginal positive significant correlation between the overall accuracy for the overall-faux pas cartoons and the GM volume in the lateral OFC at [45, 27, -9] (SVC: AAL_Frontal_Inferior_Orbital_Right, p=0.052). No significant correlation was found between the GM volume in the PFC region and the accuracy for the faux pas cartoons, as well as the comprehension cartoons. The accuracy for the non-faux pas cartoons was positively correlated with the GM volume in the lateral OFC at [-35, 48, -14], but this correlation did not survive from small volume correction (p=0.061) using the AAL_Frontal_Inferior_Orbital_Left ROI. Visual inspection showed that the peak coordinate located anterior to the AAL_Frontal_Inferior_Orbital_Left ROI. Further correction using the AAL_Frontal_Middle_Orbital_Left ROI, which covered anterior part of the lateral OFC region including BA11 region, confirmed the relationship between this GM cluster (peak MNI: -35, 48, -14) and BA11 region (SVC: AAL_Frontal_Middle_Orbital_Left, p=0.034) (see Figure 6.4, for illustration). Regression analysis on the d-prime value revealed a marginal positive correlation with the GM volume in the lateral OFC region at [45, 27, -9] (SVC: AAL_Frontal_Inferior_Orbital_Right, p=0.056). Regression analysis on the β value found no significant correlation with the GM volume in the PFC region, but whole brain exploratory analysis revealed a positive correlation between the β value and bilateral amygdala (left: -17, -4, -15, p=0.007 at cluster-level; right: 18, -1, -14, p=0.043 at cluster level) (see Figure 6.5).

Table 6.3. The VBM result of the cartoon faux pas test. The GM clusters in the PFC region showing significant correlations with the accuracy, signal detection variables (d-prime and β values) in the cartoon faux pas test between conditions (p<0.001, uncorrected for whole brain analysis, and p<0.05, FWE-corrected for SVC using different ROIs derived from the AAL atlas). Brodmann areas are approximate.

	p<0.001, uncorrected				Small Volume Correction (FWE<0.05)					
	Whole brain analysis				AAL_Inferior_Orbital		AAL_Superior_Medial		AAL_Orbital_Middle	
	k	t	MNI	Label	p	MNI	p	MNI	p	MNI
Accuracy										
Overall faux pas	21	3.54	[45, 27, -9]	BA47	0.052	[45, 27, -9]				
Non-faux Pas	16	3.53	[26, 63, 24]	BA10						
	44	3.51	[-35, 48, -14]	BA11	0.061	[-36, 50, -15]			0.034	[-35, 48, -14]
Faux Pas										
Comprehension	8	3.78	[23, 62, 30]	BA9						
	49	3.66	[-12, 48, 28]	BA9						
Signal detection										
d-prime value	21	3.54	[45, 27, -9]	BA47	0.056	[45, 27, -9]				
β value	3139	4.94	[-18, -76, -32] [a]	cerebellum						
	1179	4.77	[-17, -4, -15] [b]	amygdala						
	758	4.54	[18, -1, -14] [c]	amygdala						

[a] whole brain analysis showing cluster-level p(FWE-corr) < 0.001

[b] whole brain analysis showing cluster-level p(FWE-corr) = 0.007

[c] whole brain analysis showing cluster-level p(FWE-corr) = 0.043

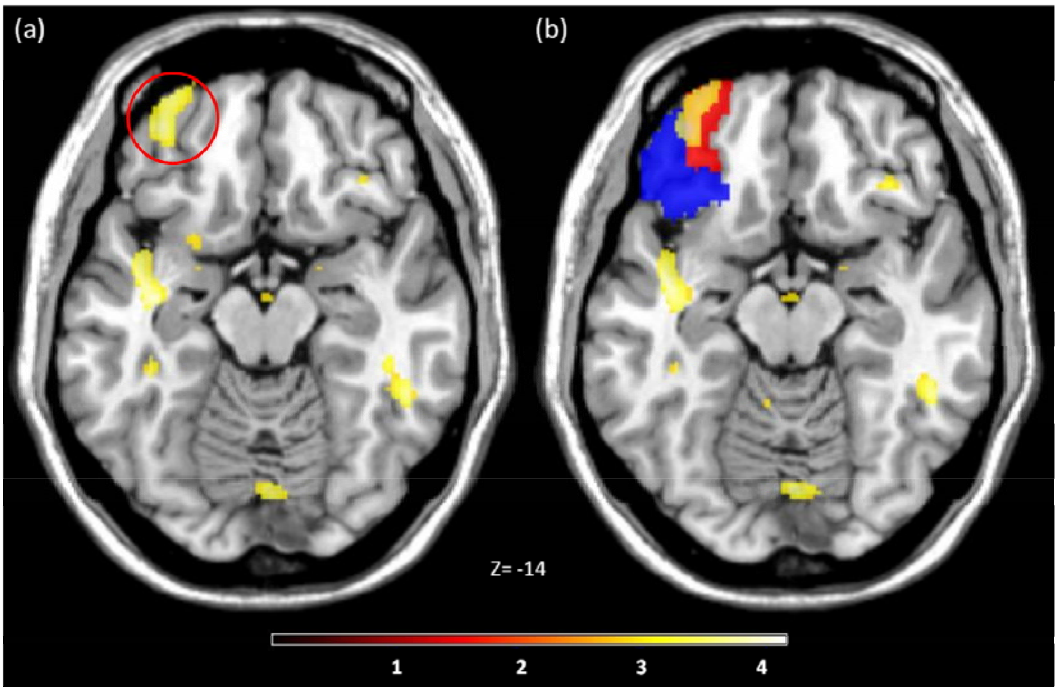


Figure 6.4. The GM volume that significantly correlated with the variables in the cartoon faux pas test. (a) Accuracy for the non-faux pas cartoons was positively correlated with a GM cluster located in the left lateral OFC region. (b) Illustration for the location of the GM cluster (coloured in yellow) that positively correlated with accuracy for the non-faux pas cartoons using two AAL atlas ROI masks: the AAL atlas ROI mask in blue colour: AAL_Frontal_Inferior_Orbital_Left, and the AAL atlas ROI mask in red colour: AAL_Frontal_Middle_Orbital_Left.

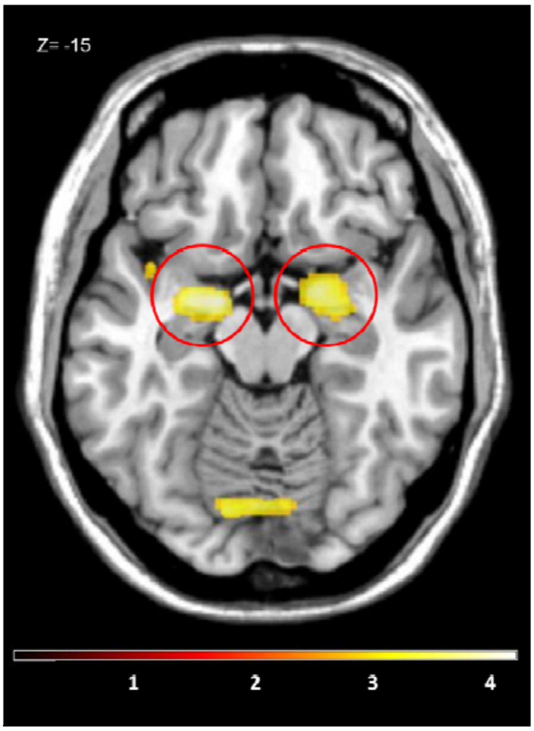


Figure 6.5. The GM volume that significantly correlated with the variables in the cartoon faux pas test, where the β value of the TD sub-group was positively correlated with bilateral amygdala.

6.7 Discussion of the VBM result in the TD sub-group

The behavioural part of the result on accuracy did not find a significant effect of condition, but the pattern remained the same as the 'baseline' performance established by 103 TD subjects. The accuracy was the highest for the non-faux pas cartoons than the faux pas and the comprehension conditions. Analysis on reaction time found consistent result as the 'baseline' performance in the TD group, where subjects in the TD sub-group responded significantly faster in the non-faux pas condition than in the faux pas condition. Together these results demonstrated that correct rejection of a faux pas, a process we hypothesised to be associated more with social evaluation, accompanied with better and faster performance than correct detection of faux pas. Due to the rightward shift of response bias (averaged β value=3.7), it was possible that the higher accuracy for non-faux pas cartoons was associated with a propensity to give *no* responses. More importantly, correlation analysis on the TD sub-group did not find a significant relationship between the accuracy for the faux pas and the non-faux pas cartoons, which was inconsistent with the finding established by the 103 TD subjects. It raised a possibility that the cognitive process supported correct identification of a faux pas might be different from the cognitive process supported correct rejection of a non-faux pas.

The VBM part of the results revealed function-structure relationships between different cortical regions and different measurements in the cartoon faux pas test. The accuracy for the non-faux pas cartoons was positively correlated with a GM cluster located in lateral BA11 at [-35, 48, -14]. This BA11 region located closely to the lesion study reported by Stone et al. (1998), where patients with bilateral OFC lesion were found to fail the faux pas test. Similarly in Roca et al. (2010), patients with lesions in the PFC region demonstrated deficits on the faux pas test compared with the controls, and the location of the BA11 cluster at [-35, 48, -14] in the current study was similar to the patient sub-group classified as 'left-lateral' lesions. Furthermore, Spitzer, Fischbacher, Hermberger, Gron, and Fehr (2007) investigated the neural correlates of norm compliance using a social punishment paradigm. The test involved two players, a victim and a violator, where the victim could punish the violator who did not follow the fairness norms in the punishment condition. The key point was to investigate how many more 'money units' would the violator transferred to the victim in the punishment condition in order to avoid even larger punishment due to violator's unfairness acts. To quantify the degree of social compliance, a 'transfer difference' score was calculated by the amount of money units invested in the punishment and the control condition, a situation where the victim was only a passive recipient. Functional MRI result revealed a positive correlation between the transfer difference score and brain activations located at [-36, 48, -10]. This relationship demonstrated by fMRI implied a special role of this BA11 region played in detecting and evaluating the potential social punishment bounded to social norms.

It is important to highlight that no significant relationship was found between any measurements and the GM volumes in the medial PFC region. Despite that brain activity in the medial PFC region was consistently observed in psychological test measuring ToM ability in fMRI studies, it is possible that the ToM ability relied more on a network instead of solely relied on one single brain region (Frith & Frith, 1999). For example, a single case study reported a patient with extensive damages to the medial PFC region failed to have any significant impairment on ToM tests including a faux pas test (Bird et al., 2004). This unique and insightful case suggested a possibility that the medial PFC region only played a special role in the ToM system, but damage to any part of the network was not sufficient to destroy its functional integrity. To justify the ToM ability as a system, we further explored the neural correlates outside the PFC region that associated with the measurements in the cartoon faux pas test, a GM cluster in BA22 at [-68, -9, 9] was found to positively correlated with the accuracy for the faux pas cartoons using a lenient threshold ($p<0.001$, uncorrected). The superior temporal gyrus, which included BA21 and BA22 regions, was identified to be one of the core regions in ToM network when considering the variations introduced by different experimental paradigm or other methodological differences (Carrington and Bailey, 2009). Together these VBM results highlighted a potential issue upon understanding ToM ability, which required investigation of the function-structure relationship between multiple cortical regions in the ToM network as a whole.

VBM regression analysis on the signal detection scores found a marginal significant relationship between the d-prime value and the GM cluster located in BA47 region (peak MNI: 45, 27, -9). In signal detection theory, d-prime value represented the sensitivity, or the distance between the mean of *signal* distribution and the mean of *noise* distribution. The larger the d-prime value indicated the greater ability to distinguish signals from noises. The observed marginal d-prime – BA47 relationship in the cartoon faux pas test indicated that subjects with larger GM volumes in lateral OFC had better capability to distinguish social situations with a faux pas from social situations without a faux pas. In previous neuroimaging studies, the lateral part of the OFC, or the ventrolateral part of the PFC region (vlPFC) was evident to involve with a range of interpersonal behaviours, which included social rejection (Sebastian et al., 2010), detecting violations of social exchange in a Prisoner's dilemma game (Rilling et al., 2008), social empathy (Kramer, Mohammadi, Donamayor, Samii, & Munte, 2010), social reasoning (Barbey, Krueger, & Grafman, 2009) and general social evaluations (Cunningham and Zelazo, 2007). Furthermore, this lateral OFC region including BA47 was also associated with ToM-related activities and was identified as part of the ToM network (Carrington and Bailey, 2009). A possible common process that underlies these various social behaviours was the ability to discriminate the authenticity of the intention from other individual. For example, a faux pas was a product of an intentional act based on some false belief. It is therefore possible that the lateral OFC region was involved with a general process that evaluates the acts came from other individual, given that social behaviours are usually opaque and misleading in some senses.

The β value, which represented the response bias that indicated the location of the internal criterion when making decisions, were found to positively correlate with the GM volume in bilateral amygdala. The linkage between amygdala and emotional processing has been long evident, where amygdala was involved with emotional learning through acquiring association with rewarding or aversive events (Gallagher and Chiba, 1996). Previous studies showed that the OFC region was anatomically interconnected with other brain regions that encoded reinforcement, including amygdala (Schoenbaum, Roesch, & Stalnaker, 2006; Roberts, 2006). Other evidences that supported the linkage between the OFC region and amygdala revealed the role of the OFC region played in representing reinforcement expectations, and related more to changes with emotional responsiveness compared with ACC (Izquierdo, Suda, & Murray, 2005; Rushworth, Behrens, Rudebeck, & Walton, 2007). It is therefore possible that TD subjects with varying size of amygdala were accompanied with different emotional responsiveness to social embarrassment, and this internal criterion led to different tendencies of *yes-* or *no*-bias when facing potential faux pas situations. Together these function-structure relationships provided some useful insights of the neural correlates in the ToM network associated with social rule violation, a complex cognition that involved both rational evaluation and emotional processing.

6.8 Atypical performance of detection to social norm violation in ASD subjects

A faux pas occurs when someone says or does something inappropriate unintentionally. To detect a faux pas, one has to represent two mental states: that the person who committed the faux pas did not know it was inappropriate, and that the person who heard it could feel hurt or embarrassed. As a result, it is seems likely that successful faux pas detection involved both cognitive and affective component.

The original faux pas test developed by Baron-Cohen et al. (1999) first established the performances of typical-developing children, and further validated the ToM nature of the faux pas test by recruiting children with Asperger's syndrome. The results highlighted that, despite the capability to pass false-belief tests, children with Asperger's syndrome had deficits on the faux pas test. Consistent findings were reported in other studies using faux pas to investigate ToM-related impairments in ASD (Baron-Cohen et al., 1999; Zalle et al., 2009) and patients with lesions in the PFC region (Stone et al., 1998; Lee et al., 2010). In the above experiments using the faux pas test, the questions in the testing phase were divided into several sub-components including faux pas detection, person identification, false belief, faux pas content, faux pas explanation, empathy or affective questions. Despite the differences on the questions, one converging result pointed out that ASD subjects with clinical diagnosis demonstrated deficits to different sub-components relating to understanding faux pas. This suggested successful faux pas responses comprised of multiple dissociable mental processes that associated with ToM, cognitive, and affective components.

In the cartoon faux pas test, we used visually presented cartoons to depict social scenarios and applied the signal detection approach to investigate the processing of faux pas detection. The behavioural results from the large TD group revealed that the accuracies for the faux pas and the non-faux pas cartoons were not correlated with each other, which implied distinct underlying processing for making 'hit' and 'correct rejection' during faux pas detection. Different and somewhat mixed results were reported between the ability to correctly identify a faux pas when there was one and correctly reject a non-faux pas when there was none. In Baron-Cohen et al. (1999) study 3, ASD children showed comparable performance as the control children on the control stories. However, in Zalla et al. (2009), using ten control stories intermixed with ten faux pas stories, the results demonstrated that the ASD group revealed an over-detection to faux pas, where they made fewer correct rejections than the TD group. In the current study, we used visually presented cartoons to depict social interactions instead of auditory stimuli, where audio tapes were used in Baron-Cohen et al., 1999, and oral presentation in Zalla et al., 2009. Furthermore, we used the data from a large group of TD subjects (n=103) to establish a valid baseline for comparison. As a result, we first examined the comprehension ability and overall ability for faux pas detection by combining the accuracy for the faux pas and the non-faux pas cartoons together, as Baron-Cohen et al. (1999) and Zalla et al. (2009) did, and then the ability to hit and correct rejection for faux pas detection separately.

From the VBM results of the TD group, we demonstrated that the accuracy for the non-faux pas cartoons was positively correlated with the GM volume in BA11 region, a structure that was seen to play an important role in faux pas studies (Stone et al., 1998; Roca et al., 2010). Furthermore, the index for sensitivity and response bias in signal detection analysis was found to associate with the GM volume in the right lateral OFC region (BA47) and bilateral amygdala respectively. This was consistent with the account that detecting a faux pas is a complex process that involved ToM ability, cognitive evaluation, and affective regulations. Interestingly, mixed results relating to different sub-components of faux pas processing were reported. In Baron-Cohen et al. (1999) study 2, the ASD children had significantly lower total scores than the control group, but no significant group difference was found for the false belief questions, a process that putatively involved with ToM-related ability. As participants were given 1 point for each faux pas identified correctly, and failure of any questions led to a score of zero, the null difference on the false belief questions implied that the significant group difference was contributed by faux pas detection or identification. However, in Zalla et al. (2009), the performances did not differ between the ASD adults and the TD adults on the detection and person identification questions, but significantly lower performances were found in ASD adults on the content, explanation, and false belief questions. With the advantage of using a signal detection approach to analyse faux pas detection, the cartoon faux pas test enabled us to compare the sensitivity and the response bias, which correlated with the size of BA47 and amygdala respectively, between the ASD and the TD group. This provided insights on the differentiation between the cognitive and the affective aspects of successful faux pas recognition. Furthermore, previous ASD studies using a signal detection approach to examine lower-level functions provided mixed findings. For example, ASD subjects were shown to have better performance in judging if the pitch of pure tones was same or different by showing higher sensitivity (Bonnel et al., 2003), which was in line with the 'Enhanced Perceptual Functioning' model proposed by Mottron et al. (2006). Yet Blake et al. (2003) used signal detection approach to measure perceptual sensitivity in ASD children, and the results demonstrated significant impairments on distinguishing biological and non-biological motions accompanying with lower sensitivity using d-prime as the index. In the cartoon faux pas test, we examined subject's faux pas ability, an advanced ToM measure, using signal detection approach. As a result, investigations on the sensitivity and the response bias of faux pas detection using d-prime and β values as indices between the ASD and the TD groups would provide useful information on higher-level cognitions relating to lower-level processing.

6.9 Behavioural result between the ASD and the TD groups

The behavioural results of the cartoon faux pas test in the ASD and the TD groups are summarised in Table 6.4.

Table 6.4. Accuracy, reaction time (msec.), and the signal detection variables including d-prime, β values in the cartoon faux pas test of the TD and the ASD groups.

	TD		ASD	
	mean	SD	mean	SD
Accuracy				
Comprehension	0.81	0.12	0.78	0.12
Faux pas - overall	0.83	0.09	0.76	0.10
Faux pas cartoons	0.80	0.12	0.76	0.16
Non-faux pas cartoons	0.86	0.15	0.77	0.19
Reaction time (msec.)				
Comprehension	9027.2	2928.5	9186.8	3125.1
Faux pas - overall	9258.6	2863.0	9893.7	3129.4
Faux pas cartoons	9509.3	2913.7	10111.6	3166.8
Non-faux pas cartoons	9007.8	2941.5	9675.9	3229.3
Signal detection variables [a]				
d-prime value	2.24	0.83	1.73	0.70
β value	3.86	4.41	2.47	4.15

[a] The formula was suggestedd by Stainslaw and Todorov (1999).

Overall faux pas vs. comprehension cartoons

The accuracy and the reaction time were entered into repeated measures ANOVA with condition (overall faux pas and comprehension) as a within-subject factor, and group (TD and ASD) as a between-subject factor. Repeated measures ANOVA on accuracy find a significant main effect of group ($F(1,131)=5.742$, $p=0.018$), and post-hoc test using Bonferroni correction identified that the TD group had significantly higher accuracy than the ASD group. No significant effect of condition ($F(1,131)=0.003$, $p=0.955$) or condition x group interaction

$(F(1,131)=2.218, p=0.139)$ was found. Repeated measures ANOVA on reaction time identified a significant effect of condition $(F(1,131)=10.406, p=0.002)$, and post-hoc test using Bonferroni correction confirmed that the reaction time was significantly slower in the overall faux pas condition than in the comprehension condition. No significant effect of group $(F(1,131)=0.623, p=0.431)$ or condition x group interaction $(F(1,131)=2.882, p=0.092)$ was found.

Faux pas vs. non-faux pas cartoons

The accuracy and the reaction time were entered into repeated measures ANOVA with condition (faux pas and non-faux pas) as a within-subject factor, and group (TD and ASD) as a between-subject factor. Repeated measures ANOVA on accuracy find a significant main effect of group $(F(1,131)=10.232, p=0.002)$, and post-hoc test using Bonferroni correction showed that the TD group had significantly higher accuracy than the ASD group. No significant effect of condition $(F(1,131)=2.154, p=0.145)$ or condition x group interaction $(F(1,131)=1.009, p=0.317)$ was found. Repeated measures ANOVA on reaction time found a significant effect of condition $(F(1,131)=13.407, p<0.001)$, and post-hoc test using Bonferroni correction confirmed that the reaction time was significantly slower in the faux pas condition than in the non-faux pas condition. No significant effect of group $(F(1,131)=1.370, p=0.244)$ or condition x group interaction $(F(1,131)=0.070, p=0.791)$ was found.

Signal detection analysis

In order to examine differences in the sensitivity and the response bias of faux pas detection between the ASD and the TD groups, independent t tests measuring d-prime and β value were conducted. The analysis found significant difference on d-prime ($t(131)=-3.054$, $p=0.002$), where the ASD subjects had significantly lower d-prime values than the TD subjects. No significant difference on the β value was found ($t(131)=1.100$, $p=0.273$). Interestingly, Levene's test for equality of variance showed that the assumption of homogeneity of variance was violated on β values ($F=4.720$, $p=0.032$), which showed that the variance in the TD group ($SD=4.40$) was significantly higher than in the ASD group ($SD=4.15$). Due to the unequal variance between groups, we used non-parametric test to examine the group difference on the β value, and Mann-Whitney test revealed a significant difference ($U=1180.000$, $p=0.049$), which indicates that the ASD had significantly lower β value than the TD group.

6.10 Discussion of the behavioural result between the ASD and the TD groups

The cartoon faux pas test used comic strips to visually present social situations, and applied a signal detection approach to address the ability of faux pas detection amongst ASD subjects, in comparison with the baseline performance established by the TD group. The between-group effect was measured in two stages, first the comprehension vs. overall ability in faux pas detection, and the second stage focused on 'correct hit' and 'correct rejection' on faux pas detection using a signal detection approach. In the first stage, ASD subjects showed comparable accuracy as TD subjects on comprehension and overall faux pas detection. This was consistent with the findings in Zalla et al. (2009), which found insignificant difference on the *detection* question between ASD and control subjects. However, when comparing the performance for faux pas and non-faux pas cartoons separately, repeated measures ANOVA found a significant main effect of group, which revealed that ASD subjects (mean=0.762) had a general deficit to correctly identify and to correctly reject a potential social embarrassment than TD subjects (mean=0.824). In Zalla et al. (2009), the ASD group tended to over-detect the control stories, where no faux pas components were included, as the non-faux pas cartoons in the current study. We therefore conducted independent t test to examine this potential over-detection effect. The result showed that ASD subject (mean=0.767) had significantly lower accuracy in the non-faux pas condition than TD subjects (mean=0.854; $t(131)=-2.529$, $p=0.013$), but no significant group difference was found in the faux pas condition (ASD mean=0.756, TD mean=0.795; $t(131)=-1.211$, $p=0.233$). Previous ASD studies using faux pas detection as a measurement for ToM-related deficit found mixed findings, where the study 3 in Baron-Cohen et al. (1999) reported no deficits in ASD children on the control stories, but Zalla et al. (2009) found over-detection to control stories in ASD adults. In the cartoon faux pas test, the results was consistent with the findings in Zalla et al. (2009) by showing selective deficits in the ASD group to non-faux pas cartoons. A possible explanation for this over-detection, as described in Zalla et al. (2009), was mainly due to the difference on the chronological age between the participants. As Happe et al. (1996) proposed, a possible reason for ASD children failed to develop an intuitive ToM ability during early years was due to mentalizing-like ability was acquired through effortful learning processes on the basis of a reasoning mechanism. It seems plausible that adults with ASD demonstrated a late-developed compensatory mechanism for lab-based social cognition tests, faux pas test in this case, and this reasoning mechanism resulted in over-detection to non-faux pas cartoons. It is important to note that we did not find a significant group difference on the accuracy for the faux pas cartoons, which was consistent with Zalla et al. (2009). This null difference was also in line with a case study reported by Shamay-Tsoory et al. (2002), which reported two adolescents with ASD were capable to recognise the faux pas stories. A possible explanation of this selective impairment was that, as shown in previous ASD studies using faux pas paradigm, successful faux pas detection comprised of multiple sub-components. For example, the ToM-related deficit might occur in questions relating to content/explanation/false belief/empathy in Zalla et al. (2009), and in justification to the inappropriate behaviours in Shamay-Tsoory et al. (2002). Furthermore, Zalla et al. (2009) demonstrated that ASD subjects had difficulties conceptualizing faux pas scenario as non-intentional acts, and unable to provide reasonable justification to understand the emotional side of the effect during social embarrassment. The lack of group effect specifically to correct identification of a potential faux pas might be due to the difference on understanding of a faux pas and/or the emotion-related processing (e.g., empathizing) between TD adults and ASD adults. Analysis on reaction time did not find any significant main effect of group or group x condition interaction. This indicated that ASD subjects did not manifest any significant slowness responding to the depicted social situations.

The cartoon faux pas test isolated the comprehension aspect, which enabled direct measurement to the ability of faux pas detection using a signal detection approach. Analysis of the d-prime value showed that the ASD group had significantly lower sensitivity than the TD group, which indicated that the ability to distinguish a faux pas from a non-faux pas was significantly poorer amongst ASD subjects. Previous ASD studies proposed an ‘Enhanced Perceptual Functioning’ model (Mottron, Dawson, Soulieres, Hubert, & Burack, 2006), which emphasised that increased perceptual processing implicated an over-functioning of a lower-level brain network. Bonnel, Mottron, Peretz. Trudel, Gallun, and Bonnel (2003) used similar signal detection approach to investigate the sensitivity on auditory processing and found enhanced pitch sensitivity in ASD subjects. In the current study, we used signal detection approach to investigate high-level cognition (e.g., faux pas detection) and identified lower sensitivity to social rule violations in ASD subjects instead. This seemingly opposite finding suggested that, despite the savant characteristics found in lower perceptual processing, this enhanced sensitivity on auditory processing did not directly contribute to higher-level cognition like faux pas detection. It is possible that lower sensitivity had a profound effect to the lower accuracy for overall-faux pas cartoons in ASD subjects, given that the distance between faux pas (signal) and non-faux pas (noise) was significantly shorter in ASD subjects than in TD subjects. On the other hand, analysis on the β values showed that response bias was more positive in the TD group than in the ASD group, which indicated a higher propensity for 'no' responses in TD subjects than in ASD subjects. This rightward shift on the criterion in TD subjects had direct influence on the accuracies for faux pas and non-faux pas cartoons. For example, it is possible that the superior performance on the accuracy for the non-faux pas cartoons in the TD group was contributed by the higher β value, whereas the ASD adults implemented a compensatory scheme that involved using a reasoning mechanism instead of ToM-related processes to solve this puzzle of social awkwardness (Happe and Frith, 1996). Furthermore, it is important to note that, the Levene's test on the β value found unequal variance between groups, and the standard deviation was significantly lower in the ASD group than in the TD group. When illustrating the β value using scatter plot, it revealed a more clustered pattern at the lower end amongst ASD individuals, with an exception of three ASD subjects who had β value larger than 13, and the rest of the 27 ASD subjects had β value below 4. In contrast, the β value was found to be in a more widespread pattern amongst TD individuals without any apparent clustered sub-groups. For comparison, the scatter plot of both d-prime and β values from both groups were illustrated in Figure 6.6. This was surprising in a sense given that ASD subjects were shown to have higher variations on behavioural measures. For example, Towgood, Meuwese, Gilbert, Turner, & Burgess (2009) used multiple case series approach to investigate the variations of behavioural performance between ASD individuals on a range of psychometric tests measuring different cognitive functions. The result demonstrate that the ASD group had significantly more supra-normal and intra-normal performances both within and between various kinds of cognitive tests. In the cartoon faux pas test, when excluding the data of the 3 'atypical' ASD subjects, the β value of the rest of the 27 ASD subjects changed drastically to mean=1.121, S.D.=0.82, compared to the original mean=2.457, S.D.=4.15. In signal detection, β value approaches 1 means subjects favoured neither *yes* response nor *no* response. The over-detection of faux pas in the ASD group, which was demonstrated by the lower accuracy for non-faux pas cartoons but not for faux pas cartoons, might result from the position of the criterion for making yes/no response when facing potential social embarrassing situations. TD subjects had higher tendency to give *no* responses and subsequently led to better performance for correct rejecting non-faux pas cartoons, whereas the majority of the ASD subjects did not show a clear bias on giving *yes* or *no* responses. Besides the biased response criterion, there are other potential explanations for the lower β value and selective deficits to non-faux pas cartoons in the ASD group. As described earlier, faux pas detection was identified as a complex cognition that involved emotion-related processing (e.g., empathizing). VBM regression analysis based on the TD sub-group in chapter6-6 found that the β value was positively correlated with the GM volumes in bilateral amygdala. Previous ASD studies using faux pas paradigm reported two ASD cases had severe empathic deficits (Shamay-Tsoory et al., 2002), and observed impairments to affective perspective taking (Zalla et al., 2009). Based on the neural correlates established by the TD sub-group, and referred the β value – amygdala linkage as ‘typical’, the un-biased neural position of criterion amongst ASD individuals might suggest an atypical regulation to emotional impact in faux pas detection.

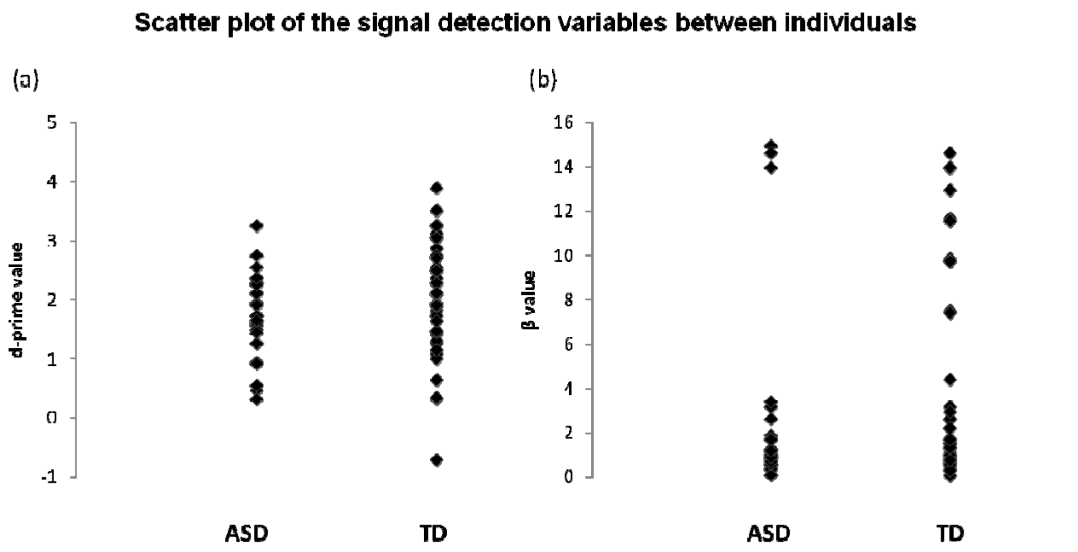


Figure 6.6. The scatter plot of the d-prime (in panel a) and β values (in panel b) of the ASD and the TD groups.

Chapter 7. PFC battery revisit

7.1 From within-test effect to between-test effect

Previous functional imaging literatures together with lesion studies provide convergent evidence showing that the PFC region, as a whole, plays an essential role in a range of psychological paradigms measuring decision-making and social cognition. In order to investigate the relationship between different PFC sub-regions and the specific cognitive processes they support, we developed PFC battery using a set of psychometric tests measuring different behaviours relating to decision-making and social cognition. The establishment of the PFC battery was based on a reverse engineering approach, where the cognitive functions that were evidently associated with the PFC region were first identified. Based on previous related paradigms, we then designed four new psychometric tests measuring the functions supported by the PFC region. In chapter 3 to 6, we introduced the four newly developed psychometric tests, reported the behavioural and VBM results in both TD and ASD groups, and discussed the potential implication of each test. The behavioural data acquired from 107 healthy TD subjects established the ‘baseline’ performance of the PFC battery, which were then used to identify the ‘atypical’ performance in the ASD group. In order to examine the function-structure relationship between specific PFC sub-regions, we further conducted VBM regression analysis to identify the neural correlates that were associated with the variables measured by the PFC battery using the data acquired from the 62 TD subjects suitable for MRI scanning. The hypothesis-testing approach using ROI-based analysis demonstrated consistent function-structure links observed in the related functional imaging literature. However, the previous PFC battery chapters of this thesis only showed the effect *within* each newly developed psychometric test. In the current chapter, we take the four psychometric tests as a whole, and explore the between-test effect of the PFC battery following various kinds of methodological approaches suggested by previous theoretical frameworks investigating PFC functions.

7.2 Is the PFC region a functionally homogeneous or heterogeneous region?

Despite convergent evidence demonstrating that the PFC region plays an important role in higher-level cognition, the mapping of specific PFC sub-regions to specific cognitive function is debatable and often yields inconsistent findings. By comparison, for other cortical functions, robust linkages are observed between brain regions like visual, auditory, motor, somatosensory cortices and the lower-level processes they support (see Kanai and Rees, 2011 for review). In the PFC region, different theories have different points of view in regard to the function-structure relationship in the PFC region. For example, in Ramnani and Owen (2004), the anterior PFC region was proposed to be a functionally homogeneous region, where "the level of functional description must accommodate the range of tasks that reliably recruit the anterior PFC, and the recruitment of that area alone should be the common link between those tasks" (p.185). On the other hand, other literatures suggest that the PFC is a functionally dissociated region where a specific type of behaviour corresponds to activation in a particular PFC sub-region (Duncan and Owen, 2000; Stuss et al., 2001; Stuss, 2007). In other words, a frequently debatable point is that it is possible that the entire PFC region is associated with a set of functions altogether, or one specific region is associated with a particular function, or a range of similar functions that inter-correlate with each other. Using functional imaging techniques, evoked brain activations provide evidence based on links between changes in regional blood flow and accompanying cognitive processes. Functional imaging findings enable us to localise the activation in an approximate brain region, but provide relatively poor spatial resolution especially when distinguishing detailed brain regions according to cytoarchitectural features. Structural-based analyses like VBM, on the other hand, provide evidence about relations between regional GM volume (or density, depending on which modulation approach is conducted) and the capability for particular mental abilities. More importantly, the ROI we used was derived from the AAL atlas, which was based on manual macro-anatomical parcellation of the single subject MNI space template brain (Tzourio-Mazoyer et al., 2002). As a result, the VBM results reported in previous chapters provide more solid evidence on the relationship between detailed brain structure and the mental abilities supported by them. Importantly, before making any further interpretations on between-test effects, it is necessary to examine the relationships between the variables between tests used for VBM regression analysis.

In chapters 3 to 6, the VBM part of the analysis found the variables derived from each test were associated with different PFC sub-regions. The identified function-structure relationships were established by small volume corrections using the ROIs derived from the AAL atlas. The observed neural correlates associated with the measurements in the PFC battery were mainly in the dorsomedial part of the PFC region and the lateral part of the OFC region. Despite the fact that the associations between the variables and the regional PFC volumes in each test were consistent with the relating fMRI findings investigating decision-making and social cognition, it is important to note that some variables derived from different tests were associated with the PFC sub-region labelled by the same ROI. For example, overall repetitiveness in the win condition, the risk rate for RA trials in the win condition, the overall repetitiveness in the loss condition of the gambling test, along with the accuracies for high-mentalizing and group conversation videos, were all associated with the same GM cluster in the dorsomedial PFC region (ROI: AAL_Frontal_Superior_Medial_Left). As mentioned in chapter 2, the rationale behind establishing the PFC battery was based on a reverse engineering approach by first identifying the cognitive function that supported by the PFC region, and then designing new psychometric tests measuring them. Here we showed that the volume of the same PFC sub-region seemed to associate with different cognitive functions. As a result, it seems necessary to consider the inter-relationships between the cognitive functions we tried to measure in the PFC battery.

The overlap between the underlying processes associated with risk-taking and inter-personal behaviours are frequently discussed from various kinds of perspectives. For example, Anderson, Bechara, Damasio, Tranel, and Damasio (1999) reported two adults with early PFC lesions and administered comprehensive neuropsychological evaluations on them. The result showed that damage to the PFC, mainly in the medial PFC region, resulted in impairment of social behaviours, insensitivity to future consequences of decisions, defective autonomic responses to punishment contingencies, and response failure to interventions. This lesion study suggested abnormal social behaviours and impairments in cognitive flexibility, a critical process for decision-making, might involve the medial part of the PFC. Additionally, Steinberg (2008) proposed a framework that discussed the relationship between social neuroscience and risk-taking behaviours. The framework proposed that one of the critical developments from adolescence to adulthood is a decline in risk-taking actions. This was accompanied with the changes in the brain's cognitive control system, which showed improvement in an individual's capacity for self-regulation, a function that is putatively substantially associated with the PFC region. This development of a neural system allows individuals to put a 'brake' on impulsive risk-seeking actions and, socially, attenuates the influence from other individuals. Together these theories indicate a potential relationship between decision-making and social cognition, as well as their common structural linkage to the medial PFC region.

Given that the aim of the PFC battery was to examine function-structure relationships in the PFC region, it is possible that the cognitive functions measured by the PFC battery were inter-correlated in some senses, and can be explained by some overlapping or common construct that accommodates a range of seemingly different mental processes. For example, Ramnani and Owen (2004) proposed five theoretical accounts that described the functions supported by the rostral PFC region, including discussing the possibility of the rostral PFC region as a functional homogeneous region. However, other researchers suggest that the PFC region is a 'versatile' structure, where similar brain activation can be observed when performing a wide range of cognitive tests (Cabeza and Nyberg, 1997; 2000; Duncan and Owen, 2000). This particular functional role of a PFC region was also motivated from single cell electrophysiology studies in monkeys, where neurons of lateral PFC appear able to code specific information and adapt their activities to different experimental contexts (Rao, Rainer, & Miller, 1997; Freedman, Riesenhuber, Poggio, & Miller, 2001; Duncan, 2001). These adaptive neural activities are commonly observed in many PFC sub-regions including the lateral PFC region and the dorsomedial PFC region (Fedorenko, Duncan, & Kanwisher, 2012), and have therefore been referred as a multiple-demand (MD) system, that organises many different kinds of behaviours (Duncan, 2006, 2010). As a result, in order to examine these possible theories regarding PFC functions, we followed the rationale of previous relating literatures and conducted statistical analysis of the data acquired from the PFC battery.

7.3 PFC region and intelligence

Early during the development of cognitive psychology, it was proposed that there is a general factor (*g* factor) that contributes to the processing of all cognitive functions (Spearman, 1904, 1927), and a potential measure of this common process is those that purport to measure general intelligence. Laboratory-based tests measuring this intelligence quotient (IQ), like Raven's Progressive Matrices (Raven and Court, 1998), provide reliable measurements on 'fluid intelligence' based on novel problem solving using different materials. Previous studies have demonstrated that people with PFC lesions can have impairments on fluid intelligence tests and have demonstrated this *g* factor can be closely associated with PFC functions (Duncan et al., 1995; 1996; 2000). Furthermore, different PFC sub-regions including BA9, 10, 46 have been identified as supporting a range of measurements of IQ (Haier, Jung, Yeo, Head, & Alkire, 2004; Barbey, Colom, & Grafman, 2013). In addition, a series of studies on a variety of frontal lobe pathologies including patients with frontal lobe lesions, Parkinson's disease, frontotemporal dementia, and schizophrenia have been conducted to examine executive functions deficits (Roca et al., 2011; 2012; 2013; 2014). The converging results showed that, although PFC supported a range of cognitive functions, a potential parcellation based on the degree of contribution of fluid intelligence was consistently observed. For one set of neuropsychological tests measuring executive function, the between-group differences became insignificant after the effect of fluid intelligence was partialled out by ANCOVA. This suggested that the deficits were associated with the core function of the MD system, which supports complex cognition during a series of attentional episodes (Duncan, 2013). In contrast, for another set of neuropsychological tests measuring multi-tasking, social cognition and risky decision-making, the between-group differences remained significant after the effect of fluid intelligence was partialled out. This indicated that the deficits cannot be explained by the general factor and may relate to other PFC regions outside the frontal-parietal MD system (Duncan, 2010). In previous PFC battery chapters, we developed new psychometric tests measuring different aspects of decision-making and social cognition, and identified the deficits observed in the ASD group, compared with the baseline performance established by the TD group. Previous ASD studies revealed that people with ASD had both structural and functional abnormalities in the medial PFC region (Waiter et al., 2004; Carper and Courchesne, 2005; Schmitz, Rubia, Daly, Smith, Williams, & Murphy, 2006; Courchesne, Campell, & Solso, 2011; McAlonan et al., 2005; Gilbert, Gollowitzer, Cohen, Burgess, & Oettingen, 2009). Therefore, before examining the underlying processes measured by the PFC battery, it seems necessary to first test the contribution of this general factor to the PFC battery performance. As a result, in the current chapter, we re-examined if the between-group difference still existed after the general intelligence effect (the NART score, in the current study) was partialled out by ANCOVA. Furthermore, we examined the relationships between the experimental variables across different PFC battery tests that significantly correlated with the NART score, and further investigated the neural correlates that associated with the NART score. The NART is a test of irregular word reading, which is of course a test of crystallized rather than fluid intelligence. However, here it is used as a proxy for fluid IQ since in a healthy population they should be highly correlated.

7.4 PFC region and gender

Compared with the series of studies conducted by Roca et al., (2011; 2012; 2013; 2014) examining executive functions deficits in neurological patients, in the previous PFC battery chapters in this thesis we recruited adults diagnosed with ASD, a clinical group that typically show deficits on decision-making and social cognition, as well as structural abnormality in the PFC region. More specifically, ASD is a gender-linked developmental disorder encompassing impairments in social interaction, verbal and non-verbal communication, and gender was evident to have profound effect on brain structure and functions in ASD subjects (Lai et al., 2011; 2013). Similarly, in TD subjects, a widely-cited VBM study of 465 normal adults revealed that females, compared with males, have significantly increased GM volume in the right lateral orbital region and cingulate gyrus (Good et al., 2001). It is important to note that these two PFC sub-regions were discovered to associate with a range of experimental variables in the PFC battery. In previous studies investigating PFC functions from developmental perspective, it was reported that males and females have age-related changes across the period of adolescence in the medial PFC region (Giedd et al., 1999; Mills et al., 2014). The transition period of adolescence can be considered as a preparation stage for fulfilling a person’s role as an adult. For example, daily behaviours relating to social interactions change dramatically during adolescence, and functional changes have also been discovered between adolescence and adulthood in pattern of brain activity within the social brain network (Frith, 2007; Blakemore, 2008), a theoretical framework involving the medial PFC region. In TD subjects, gender-related differences were observed in a range of cognitive tests including risky decision-making (e.g., IOWA gambling test, see van den Bos et al., 2013) and alteration of social interactions (Bussey and Bandura, 1999). Previous studies found that females score significantly higher than males in tests required perspective-taking, the capacity to understand others' mental states, and the faux pas test (Stiller and Dunbar, 2007; Baron-Cohen et al., 1999). When comparing risk-taking behaviours, Lee, Chan, Leung, Fox, & Gao (2009) used a Risky-Gains test and showed that female participants, compared with male participants, make significantly more safe options. It appears that converging evidence has demonstrated that gender-related difference, both functionally and structurally, has strong linkage to the PFC region. As a result, we hypothesised that both TD and ASD subjects might show gender-related difference on the behaviours measured by the PFC battery. In order to examine this possibility, we examined the group x gender interaction on the variables associated with risky decision-making (the overall risk rate and the overall repetitiveness in the gambling test) and social cognition (the accuracies for mentalizing and faux pas detection). Furthermore, we also examined the neural correlates that showed gender-related differences within the PFC region, and investigated the relationships between the variables showing gender difference in the PFC battery.

7.5 PFC region and the function is supported

Besides investigating the potential contributions from mediating factors such as general intelligence and gender discussed earlier, it is also important to answer questions concerning the exact underlying processes the PFC battery measured. The establishment of the four psychometric tests included in the PFC battery focused on two seemingly different functions, one was decision-making and the other social cognition. We discussed the previous lesion and neuropsychological evidence suggesting the overlap between these two domains, and as a result, it is possible that the number of underlying processes we measured in the PFC battery were fewer that we expected. In other words, a rather radical possibility was that the four tests actually measured one single complex construct. Alternatively, it was also possible that the mental processes associated with the four different tests were inter-correlated with each other. For example, to do or not to do a certain action under a specific context is probably the most common decision in everyday life, and we were often required to make decisions under uncertain situations. In laboratory-based conditions, gambling paradigms provided opportunities to receive rewards or punishments by making voluntary decisions after evaluating potential risks (e.g., the win and the loss conditions in the gambling test). However, not every decision we made was under uncertainty, for example, the decisional processes based on one's own internal metric can be 'risk-free'. Daily situations like choosing to start a conversation with a stranger in a bar (e.g., the personality condition in the referential judgment test) or deciding to lift a heavy grocery bag with your preferred hand (e.g., the weight condition in the referential judgment test) were the kinds of decisions without external uncertainty. These decision-making processes could be accomplished solely relied on one's own internal construct. The idea of this personal construct proposed by George Kelly described individual's understanding toward events that were influenced by one's own anticipation. Specifically, processing a construct related to 'self' was argued to be processed differently from other constructs, and the idea of self-referential processing could be viewed as a mental process that people referred to themselves as an anchor, or reference point. In daily situations, some decisions we make might involve others, and the ability to consider another's perspective is an important skill of our lives. As a result, making inferences about another's mind is a kind of social behaviour requiring inter-personal judgment (Mitchell et al., 2005). The ability to make correct inferences about another person's mental states or belief is one of the abilities associated with 'Theory of Mind' (e.g., the accuracy for making correct decisions in the video mentalizing test). When social groups become bigger, in order to have harmonic inter-personal relationships with other members, people tend to consider some social behaviour as 'standard', and view them as social norm. As long as there are standardised behaviours, there are violations to the social norm as well. Therefore, it is essential for individuals to detect inappropriate social behaviours that make people feel embarrassed (e.g., the accuracy for detecting faux pas and correct rejecting non-faux pas in the cartoon faux pas test). The internal standard that determines embarrassment from non-embarrassment and the criterion that distinguished norm from violation could be considered as the ability to detect a faux pas using a signal detection approach. As described above, despite the four psychometric tests measuring different aspects of functions supported by the PFC region, the underlying processes we measured in the PFC battery linked with each other in some senses. Moreover, the VBM part of the results reported in each test validated the function-structure associations in different PFC sub-regions using a hypothesis-testing approach. As suggested earlier, it is critical to understand the inter-relationships between the underlying processes measured by the variables in each test. In order to investigate how many independent cognitive components measured in the PFC battery, we conducted principal component analysis (PCA), a dimension reduction method, to identify the potential components across the four psychometric tests included in the PFC battery.

7.6 The PFC region and individual differences

In terms of the acquired deficits in patients with neurological disorders, the observed atypical performance can vary case-by-case. Structurally, there is no doubt that there are no two brains that are completely identical, and the variation between pathological patients is expected to be greater, which may lead to greater observable difference in their symptoms. In the cognitive neuropsychology literature, famous single-case studies like Phineas Gage who suffered from injuries in the PFC region provide fruitful insights into human cognitive functions. Cognitive neuropsychology not only focusses on understanding how the normal or typical cognitive network is organised, but also investigates atypical individuals, which provide strong evidence on the relationship between brain structure and cognition. The single-case approach of pathological studies has studied psychometric tests in a wide range of domains including perception, memory, language, and executive functions (see Shallice, 1988 for review).

In previous PFC battery chapters, the pathological group we investigated was adults with ASD, a neurodevelopmental disorder characterised by repetitive mannerisms, impairments in social interactions, as well as verbal and non-verbal communication difficulties. Previous investigators have proposed that it seems unlikely that there is one single deficit that covers the wide range of ASD symptoms demonstrated on cognitive tests, but instead that there are complex patterns of associations of deficits between and within domains (Happe, Ronald, & Plomin, 2006). Evidences from neuroimaging studies suggests that people with ASD have an abnormal pattern of functional specialisation in the PFC region (Gilbert, Meuwese, Towgood, Frith, & Burgess, 2009) and outside the PFC region (Pierce, Muller, Ambrose, Allen, & Courchesne, 2001). In previous ASD studies, the deficits were typically identified by using between group statistics across a range of cognitive domains. However, this traditional approach does not always yield converging results, and studies using different psychometric tests measuring the same construct have led to inconsistent findings, with some finding significant deficits yet some finding null results. Hill (2004) reviewed the literature investigating deficits relating to executive functions in ASD and found mixed results. In ToM tests, on the other hand, Baron-Cohen et al. (1985) developed the classic ‘Sally-Anne’ test and found children with ASD failed this test by assessing false belief compared with typical-developing children. However, not every ASD children failed the ‘Sally-Anne’ test in Baron-Cohen et al. (1985), and mixed findings on ToM deficits amongst ASD individuals is also evident in numerous subsequent studies (Bowler, 1992; Happe, 1995). Thus even with the feature that most theorists these days argue is fundamental to ASD (ToM deficits), the evidence shows some inconsistencies.

Perhaps the only converging outcome is that ASD individuals demonstrate an uneven pattern of cognitive strengths and weakness (Frith, 2003). The reported deficits in Frith (2003) included poor language comprehension, working memory deficits, failures to use context to support memory, poor memory for complex visual information, difficulties with planning, and problems with set shifting attention. On the other hand, strengths were also reported in spatial reasoning, abstract problem solving, and performances required focussed attention. A possible explanation was the experimental design of the psychometric tests implemented. Happe and Frith (2006) reviewed over 50 ASD studies and found some paradigms generate consistent results but some lead to inconsistent or even negative findings. Another possible explanation for the disparity of the discoveries in ASD studies is that the clinical diagnosis might incorporate subjects with high variations in strengths and weakness across different domains, perhaps suggesting multiple distinct sub-groups amongst the recruited ASD population. Furthermore, it is also possible that the attentional deficits in ASD cause perturbations during test administration. Some researchers have proposed that the impaired performances in ASD are due to deficits in some fundamental processes including language comprehension, perception or short-term attention, where minor difference lead to major effects on performance. The sources of the attentional variations include deficits in using social cues efficiently compared with controls, or the enhanced performances on tests requiring focussed attention. It is likely that these unpredictable impairments during processing lower-level features (e.g., stimulus materials) affect performances particularly when using paradigms targeted at higher-level cognitions (e.g., decision-making and social cognition).

The variation in behavioural performance on the variables measured by the PFC battery was also found in the ASD group. Some significant atypical performances in the ASD group were supra-normal, and some were sub-normal, compared with the baseline established by the TD group. This suggests a marked heterogeneity of abilities in the ASD group across a range of domains supported by the different PFC sub-regions. Analysis at the group level can only reveal the abnormality in a general sense, instead of discovering variations between each ASD individual. Towgood et al. (2009) therefore used a multiple case series approach to analysis to demonstrate the greater functional heterogeneity of the ASD subjects. However, the psychometric tests included in Towgood et al. (2009) covered a wide range of functions. In the current study, all the psychometric tests we conducted measured functions putatively supported by different PFC sub-region evident by VBM regression analysis in previous PFC battery chapters. As a result, we followed the rationale described in Towgood et al. (2009) and examined the size of the individual differences within the ASD subjects. More detailed procedure is described in the later method section below.

7.7 PFC region and potential diagnostic tool for predicting ASD population

The evidence provided by the single-case studies was established by an empirical procedure with several stages of scientific examinations. First, the core cognitive deficits of the pathological subject needed to be identified, and a theoretical model was proposed to describe the relevant cognitive network that putatively associated with the observed symptoms. Then intensive investigations involving a series of psychometrical tests seeking to isolate the underneath processes that underpinning the impairment were conducted, and in the meantime excluding other possibilities or controlled for potential confounds. As a result, the process of the investigation required a range of psychometric tests that measuring the latent construct that tapped on the deficits, and eventually developed reliable psychometric measurements that had strong power to predict group membership when no further information was provided. In order to achieve this, we conducted binary logistic regression analysis to identify the measurements that had good predictive power for distinguishing ASD subjects from TD subjects.

7.8 Experimental hypotheses and the variables included for analyses

The aim of this chapter was to investigate the between-test effects of the PFC battery. This included the analyses of 1) the contribution of general intelligence to between-group difference; 2) the group x gender interaction on variables measuring decision-making and social cognition; 3) the identification of potential components in the PFC battery; 4) the single-case approach analysis to the atypical performance in the ASD group; 5) identification of the diagnostic tools for identifying ASD subjects. In order to describe the variables in each test briefly, we used abbreviation to refer to each variable in the following sections. In the gambling test, or the G test, the overall risk rate, overall repetitiveness, and overall reaction times were referred as G_wrate, G_lrate, G_wrep in the win condition, and G_lrep, G_wrt and G_lrt in the loss condition. In the referential judgment test, or the R test, the consistency score and the overall reaction times were referred as R_pscore, R_prt in the personality condition, and R_wscore and R_wrt in the weight condition. In the video mentalizing test, or the M test, the accuracies for high-mentalizing, low-mentalizing, dyad conversation, and group conversation videos were referred as M_highacc, M_lowacc, M_dyadacc, M_groupacc, and the reaction times were referred as M_highrt, M_lowrt, M_dyadrt, M_grouprt. In the cartoon faux pas test, or the F test, the accuracies for comprehension, faux pas, and non-faux pas cartoons were referred as the F_compacc, F_fpacc, F_nfpacc, and the reaction times were referred as F_comprt, F_fprt, and F_nfprt. The d prime and β score representing the sensitivity and the response criterion were referred as F_dprime and F_β respectively.

7.9 Methods of the between-test analysis

Subjects

In order to have equal numbers of subjects for examining between-test effect, we included the 103 TD adults (55 males, 53 females) and 30 adults with ASD (20 males, 10 females) having complete data for all the four psychometric tests in the PFC battery for statistical analyses. No significant differences were found between the age and NART between the TD and the ASD groups (see Table 7.1). All the 30 ASD subjects had IQ measured with the WAIS and had Autism Spectrum Quotient (AQ: Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). In the TD group, 49 TD subjects had WAIS and 35 had AQ score.

Table 7.1. The demographic information of TD and ASD subjects included for the between-test analysis in chapter7.

	TD group	ASD group	p-value
Subject number	103	30	
male/female	55	20	0.216 [c]
Age	32.41	36.1	0.098
NART	115.82	114.3	0.295
Verbal IQ [a]	113.8	116.4	0.416
Performance IQ [a]	111.12	110.1	0.896
AQ [b]	16.11	35.3	<0.001

[a] n=49 in the TD group

[b] n=35 in the TD group

[c] The significance was calculated using Fisher's Exact test

PFC battery variables for analysis

All the variables included for statistical analyses in the current chapter, including ANCOVA, ANOVA, PCA, multiple case series approach analysis, and binary logistic regression analysis, were derived from the four tests in the PFC battery. However, based on the purpose and constraint for different statistical analysis, the variables and the format of the variables included were different.

For PCA, any computed variables (or linearly transformed variables) were excluded, due a correlation of almost 1 with the raw, untransformed values. For example, in the video mentalizing test, the variables included for PCA were the accuracies for high-mentalizing dyad, high-mentalizing group, low-mentalizing dyad and low-mentalizing group videos instead of the averaged accuracies for the high vs. low-mentalizing and/or dyad vs. group conversation videos. Similarly, in the cartoon faux pas test, d-prime and β values were not included for PCA. In the gambling test, given that the repetitiveness variables were calculated by a V-shaped transformation, not linearly transformed, the repetitiveness variables were included for PCA. Furthermore, the aim of PCA was to examine the potential construct in the PFC battery, the variables included were organised in the same direction. In order to achieve this, all the reaction time variables were mirrored as the negative values, e.g., turned a reaction time of 15000 msec. as -15000 msec. As a result, the higher the values for any non-reaction time variable indicated better performances, and the higher the values for any reaction time variable represented better performances as well. When it comes to between groups PCA, given that the ASD group were subjects diagnosed with deficits on social interactions and stereotyped behaviours, it is possible that the ASD and the TD groups considered the observable variables in the PFC battery in a distinct way. Hence, we conducted PCA for TD and ASD subjects separately.

For all the rest of the analyses, including ANCOVA, ANOVA, multiple case series approach and binary logistic regression analysis, we included transformed variables and focused on identifying factors that distinguished group difference and membership. For example, in the video mentalizing test, robust findings revealed that people with ASD had selective difficulty on responding to social situation relying on high intentionality. We used averaged accuracy and reaction time collapsing the complexity factor and examined the effect between videos with high vs. low intentionality. In the cartoon faux pas test, we included the d-prime and β values for analysis, given that previous studies identified signal detection related atypicality amongst ASD subjects. The variables included for each statistical analysis were listed in Table 7.2.

Table 7.2. The variables in each test of the PFC battery that included in the between-test analysis in chapter7.

PFC battery test	Variables included for statistical analysis
The gambling test	G_wrate, G_lrate, G_wrep, G_lrep, G_wrt, G_lrt
The referential judgment test	R_pscore, R_wscore, R_prt, R_wrt
The video mentalizing test [a]	M_highacc, M_lowacc, M_highrt, M_lowrt
The cartoon faux pas test [b]	F_fpacc, F_nfpacc, F_compacc, F_fprt, F_nfprt, F_comprt, F_dprime, F_beta

[a] M_highdyadacc, M_highgroupacc, M_lowdyadacc, M_lowgroupacc, M_highdyadrt, M_highgrouprt, M_lowdyadrt, M_lowgrouprt for PCA

[b] F_dprime, F_beta were excluded for PCA

7.10 Results of the between-test analysis

ANCOVA analysis of general intelligence

Behavioural result

The results of all the between-group effects in the four psychometric tests without partialling out the NART score were reported in the previous chapters. The ASD group had significantly slower reaction time, compared with the TD group, in G_wrt, G_lrt, R_prt, R_wrt, and M_highrt. In addition, compared with the TD group, the ASD group demonstrated significantly higher scores in G_wrep, and had significantly lower scores in M_highacc, F_nfpacc, and F_dprime. Before conducting ANCOVA with NART as the controlled variable, we first examined the correlations between the NART score and each variable in the TD and the ASD groups. Spearman rank-order correlation analysis revealed that G_wrep was the only variable that had significant relationship with the NART score in both groups. The NART score was significantly correlated with G_wrt, G_lrt, M_highacc, F_nfpacc, F_dprime only in the TD group, but not in the ASD group (see Table 7.3.). Next, we used ANCOVA to partial out the contribution of IQ (the NART score in the current study), and the result showed that all the variables that demonstrated significant group difference remained significant after the NART score was introduced as a covariate of non-interest.

Table 7.3. The mean of the PFC battery variables showing significant group effect and their correlations between the NART score, as well as the significance before and after the NART score was introduced as a covariate of non-interest in ANCOVA model.

PFC battery variable	mean (ASD group)	mean (TD group)	Spearman's correlation with NART (TD group)	Spearman's correlation with NART (ASD group)	Main effect of group: *before* NART was introduced as a covariate	Main effect of group: *after* NART was introduced as a covariate
G_wrt (msec.)	1671.1	1389.5	-0.241 *	0.255	p=0.007	p=0.007
G_lrt(msec.)	1767.8	1481.0	-0.262 **	0.123	p=0.035	p=0.028
G_wrep	81.15	72.38	0.261 **	0.368 *	p=0.017	p=0.006
R_prt(msec.)	2685.5	1947.5	-0.092	-0.022	p=0.002	p=0.002
R_wrt(msec.)	2063.1	1562.8	-0.145	0.001	p<0.001	p<0.001
M_highacc	0.63	0.74	0.236 *	-0.107	p<0.001	p=0.001
M_highrt(msec.)	13485.4	12013.9	0.072	0.332	p=0.017	p=0.026
F_nfpacc	0.77	0.85	0.254 **	0.008	p=0.013	p=0.019
F_dprime	1.73	2.23	0.309 **	0.059	p=0.003	p=0.005

* p<0.05 (two-tailed); ** p<0.01 (two-tailed)

VBM result

In VBM analysis, when putting age, gender and total intra-cranial volume as covariate of no interest in the regression model, no GM cluster were significantly correlated with the NART score in both positive and negative directions.

Repeated measures ANOVA on group x gender

Repeated measures ANOVA models were set up using group (TD vs. ASD) and gender (male vs. female) as the between-subject factor, and the experimental condition in each of the four tests in the PFC battery as the within-subject factor.

The gambling test

The analysis of the overall risk rate in the win and the loss conditions showed only significant main effect of condition ($F(1,129)=17.352$, $p<0.001$), where the overall risk rate in the loss condition was significantly higher than the overall risk rate in the win condition. No significant main effect of group, gender, and any interactions were found. The analysis of the overall repetitiveness showed a significant main effect of condition ($F(1,129)=43.551$, $p<0.001$), where the overall repetitiveness was significantly higher in the win condition than in the loss condition. The analysis did not find a significant effect of gender ($F(1,129)=3.622$, $p=0.059$). Importantly, repeated measures ANOVA revealed a significant condition x group x gender interaction ($F(1,129)=17.385$, $p<0.001$). Follow-up analysis showed that the group x gender interaction was only significant in the loss condition ($F(1,129)=7.883$, $p=0.006$), but not significant in the win condition ($F(1,129)=1.409$, $p=0.237$).

Independent t test confirmed that the significant interaction in the loss condition was contributed by a significant effect of gender in the ASD group (male: 74.69; female: 50.75; $t(28)=2.357$, $p=0.026$), but the gender effect was not significant in the TD group (male: 65.51; female: 61.91; $t(101)=-0.498$, $p=0.619$) (see Figure 7.1, for illustration).

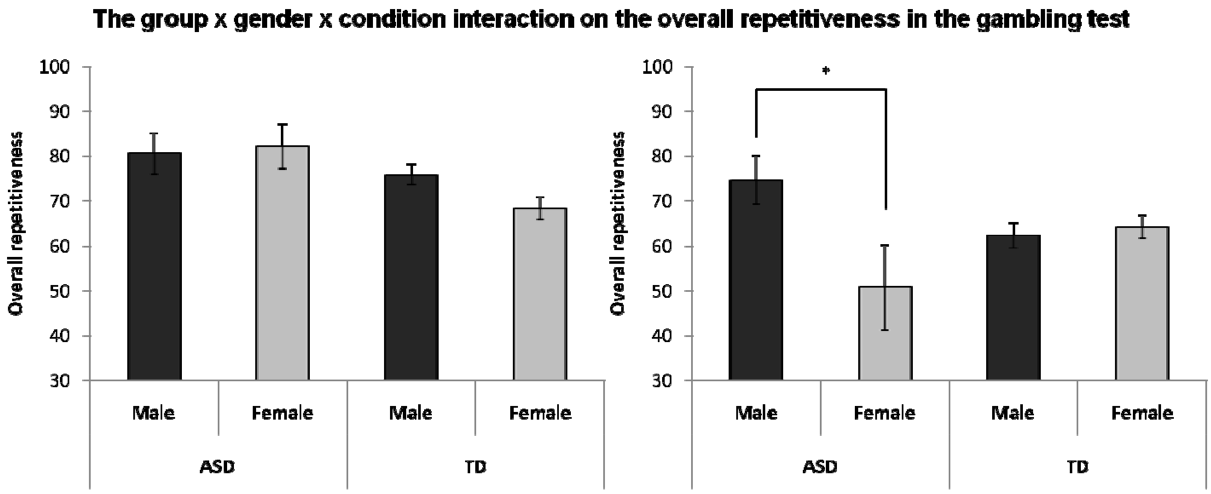


Figure 7.1. The significant group x gender x condition interaction on the overall repetitiveness in the gambling test. The group x gender interaction in the win condition was illustrated in the left panel, and the group x gender interaction in the loss condition was demonstrated in the right panel.

The referential judgment test

The analysis showed a significant main effect of condition (F(,129)=11.557, p=0.004), where subjects had higher consistency score in the weigh condition than in the personality condition. No significant main effects of group, gender, and any interactions were found.

The video mentalizing test

Analysis of the accuracy in the video mentalizing test revealed a significant main effect of group (F(1,129)=8.933, p=0.003), where the ASD group had significantly lower accuracy than the TD group in general. Repeated measures ANOVA also demonstrated a marginal significant condition x group interaction (F(1,129)=3.788, p=0.054). Independent t test confirmed that the effect was driven by significant group difference to high-mentalizing videos (ASD: 0.63; TD: 0.74; t(131)=-3.646, p<0.001), but the group effect was not significant to low-mentalizing videos (ASD: 0.68; TD: 0.72; t(131)=-1.215, p=0.226).

The cartoon faux pas test

Repeated measures ANOVA measuring the accuracy found a significant main effect of group (F(1,129)=7.614, p=0.007), which showed that TD subjects made significantly more accurate response to the cartoons than ASD subjects did in general. No significant gender, condition, and any interactions were found. Analysis of the d-prime value found a significant main effect of group (F(1, 129)=7.865, p=0.006). No significant gender and group x gender interactions were found. Analysis of the β value did not find any significant effect of group, gender, and group x gender interaction.

VBM analysis of gender in the TD sub-group

When putting age and total intra-cranial volume as covariate of no interest in the regression model, VBM analysis found no GM cluster survived from FWE-corrected p<0.05 threshold in the PFC region in the male > female comparison. On the other hand, when comparing female > male, VBM analysis identified a GM cluster in the medial PFC region (k=2423, p(FWE-corrected)<0.001, Z=4.28, peak MNI coordinate=-15, 38, 24). This massive GM cluster extended from BA9 posteriorly to BA6 region (see Figure.7.2, for illustration).

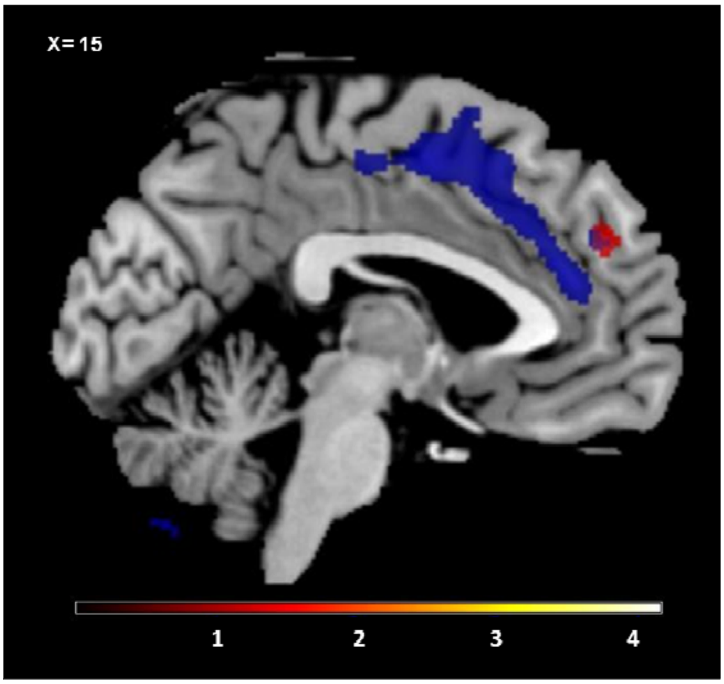


Figure 7.2. The GM cluster that was significant in the female > male contrast in the TD-subgroup. Blue colour: whole brain analysis (FWE p<0.05) showing female > male; Red: GM cluster positively correlated with the G_wrep variable in the TD sub-group.

Principal component analysis

The principle component analysis was conducted in two steps. First, we conducted PCA in the within-test level to isolate the independent factors in each psychometric test. Then we conducted PCA in the between-test level to examine the dissociable factor in the PFC battery as a whole. We used the principal components method for data reduction and set the eigenvalues greater than 1 as the inclusion threshold for potential components. For any components having eigenvalues greater than 1, the factor rotation method we implemented was the Varimax option, which demonstrated the factors that were orthogonal with each other. The factors having absoluate values above 0.5 in the rotated component matrix were categorised as the same component. The eigenvalues, variance explained, and the variables included in each newly-defined factor were summarised in Table 7.4, where the panel (a) showed the result of the TD group, and the panel (b) demonstrated the result of the ASD group.

Table 7.4. The within-test PCA and the between-test PCA result of the TD group (panel a) and the ASD group (panel b). The extracted component, eigenvalue, accumulated variance, as well as the newly-labelled factor name were summarised in each column

(a) TD group	Component	Eigenvalues	Variance (%)	Cumulative (%)	Variables (factor name)
Within-test PCA					
The gambling test					
	1	1.96	32.58	32.58	G_wrt, G_lrt (G_reactiontime)
	2	1.45	24.17	56.75	G_wrep, G_lrep (G_repetitiveness)
	3	1.03	17.11	73.85	G_wrate, G_lrate (G_riskrate)
The referential judgment test					
	1	1.66	41.44	41.44	R_prt, R_wrt (R_reactiontime)
	2	1.22	30.43	71.87	R_pscore, R_wscore (R_consistency)
The video mentalizing test					
	1	3.63	45.36	45.36	M_highdyadrt, M_highgrouprt, M_lowdyadrt, M_lowgrouprt (M_reactiontime)
	2	1.27	15.84	61.20	M_highgroupacc, M_lowdyadacc, M_lowgroupacc (M_high+lowmentalizing)
The cartoon faux pas test					
	1	3.02	50.39	50.39	F_fprt, F_nfprt, F_comprt (F_reactiontime)
	2	1.13	18.80	69.20	F_fpacc, F_compacc (F_fpacc+compacc)
	3	1.04	17.38	86.58	F_nfpacc
Beween-test PCA					
	1	2.31	23.09	23.09	G_reactiontime, R_reactiontime
	2	1.91	19.11	42.20	M_reactiontime, F_reactiontime
	3	1.16	11.62	53.82	G_repetitiveness, M_high+lowmentalizing, F_nfpacc
	4	1.04	10.44	64.26	R_consistency, F_fpacc+compacc

[a] negative correlation

(b) ASD group	Component	Eigenvalues	Variance (%)	Cumulative (%)	Variables (factor name)
Within-test PCA					
The gambling test					
	1	1.88	31.34	31.34	G_wrt, G_lrt, G_lrate (G_reactiontime+lrate)
	2	1.74	28.99	60.32	G_wrate
	3	1.16	19.25	79.57	G_wrep, G_lrep (G_repetitiveness)
The referential judgment test					
	1	1.66	41.40	41.40	R_prt, R_wrt (R_reactiontime)
	2	1.22	30.61	72.01	R_pscore, R_wscore (R_consistency)
The video mentalizing test					
	1	3.98	49.75	49.75	M_highdyadrt, M_highgrouprt, M_lowdyadrt, M_lowgrouprt (M_reactiontime)
	2	1.26	15.80	65.55	M_lowdyadacc, M_lowgroupacc (M_lowmentalizing)
	3	1.03	12.83	78.38	M_highdayaacc, M_highgroupacc (M_highmentalizing)
The cartoon faux pas test					
	1	2.95	49.15	49.15	F_fprt, F_nfprt, F_comprt (F_reactiontime)
	2	1.27	21.19	70.34	F_fpacc, F_nfpacc [a] (F_fpacc+nfpacc)
	3	1.03	17.14	87.48	F_compacc
Beween-test PCA					
	1	2.63	23.94	23.94	G_reactiontime+lrate, R_reactiontime, M_reactiontime, F_reactiontime
	2	1.93	17.56	41.50	M_highmentalzing, F_compacc
	3	1.66	15.07	56.57	M_lowmentalizing, F_fpacc+nfpacc
	4	1.47	13.37	69.94	G_wrate, R_consistency [a]

[a] negative correlation

Step 1: Within-test PCA

The gambling test

PCA of the TD group extracted three components. The first factor included the overall reaction time in both conditions (the G_reactiontime factor), the second factor included the overall repetitiveness in both conditions (the G_repetitiveness factor), and the third one included the overall risk rate (the G_riskrate factor). On the other hand, PCA of the ASD group also identified three components. The first factor included the overall reaction time in both conditions, as well as the overall risk rate in the loss condition (the G_reactiontime+loseriskrate factor). The second factor included the overall risk rate in the win condition (the G_winriskrate factor), and the overall repetitiveness in both conditions were identified as the third factor (the G_repetitiveness factor).

The referential judgment test

PCA extracted two unrelated components in both the TD and the ASD groups. The first factor included the overall reaction time in both conditions (the R_reactiontime factor), and the second factor included the consistency score in both conditions (the R_consistency factor).

The video mentalizing test

In the TD group, PCA extracted two uncorrelated components. The first factor included the reaction time in all the four conditions (the M_reactiontime factor), and the second factor included the accuracy in the high-mentalizing group, low-mentalizing group, and low-mentalizing dyad conditions (the M_high+lowmentalizing factor). PCA of the ASD group identified three different components. The first factor included the reaction time in all the four conditions (the M_reactiontime factor). Interestingly, PCA extracted the accuracy for low-mentalizing group and low-mentalizing dyad videos as the second factor (the M_lowmentalizing factor), and the accuracy for high-mentalizing group and high-mentalizing dyad videos as the third and separate factor (the M_highmentalizing factor).

The cartoon faux pas test

PCA of the TD group extracted three separate components. The first factor included the reaction time in the three conditions (the F_reactiontime factor), the second factor included the accuracy for the faux pas and the comprehension cartoons (the F_fpacc+compacc factor), and the third factor is the accuracy for the non-faux pas cartoons (the F_nfpacc factor). In the ASD group, PCA identified three isolate components. The first component included the reaction time in the three conditions (the F_reactiontime factor), the second component included the accuracy for the faux pas and the non-faux pas cartoons in a negative relationship (the F_fpacc+nfpacc factor), and the accuracy for the comprehension cartoons was identified as the third component (the F_compacc factor).

Step 2: Between-test PCA

Next, we used the saved factor scores calculated by the within-test PCA in the first step, and conducted a between-test PCA using those newly obtained factor scores as the variables (see Table 7.4, for summary).

The between-test PCA extracted four components in the TD group. The first component included the G_reactiontime and the R_reactiontime factors, the second component included the M_reactiontime and the F_reactiontime factors. Furthermore, the G_repetitiveness, the M_high+lowmentalizing, the F_nfp factors were extracted as the third component, and the R_consistency, as well as the F_fpacc+compacc factors were identified as the fourth component. In the ASD group, PCA also revealed four but different components. The first component included the G_reactiontime+lrate, the R_reactiontime, the M_reactiontime, and the F_reactiontime. The second component included the M_highmentalizing and the F_compacc components. The third component included the M_lowmentalizing and the F_fp+nfp components. Lastly, the G_wrate and the R_consistency factors were the fourth and negatively correlated component.

Multiple case series analysis

In previous PFC battery chapters, the between-group results showed that the ASD group had some significant supra-normal performances and some intra-normal performances, compared with the baseline performance in the TD group. This high variation of performance demonstrated a marked heterogeneity of abilities across a range of cognitive functions supported by the different PFC sub-regions in the ASD group. However, the tradition statistical analysis of group level can only provide an inaccurate perspective to this functional heterogeneity, rather than demonstrating the unique variations between each ASD individual. In order to investigate the unique variations of performance in the ASD group statistically, we followed the principle described in Towgood et al. (2009) and conducted the multiple case series analysis to demonstrate 1) each ASD individual's performance compared with the normative sample, and 2) the performances across different tests within each ASD individual. One of the critical differences between Towgood et al. (2009)'s study and current study was that the PFC battery was not a standardised psychometric tool. The various kinds of well-established psychometric measurements included in Towgood et al. (2009) had reliable norm to define the so-called 'typical' performance. To compensate this difference, we used a distribution-free approach to set up our cut-off criterion to draw the line between 'typical' and 'atypical' performance, instead of using standard deviation as in Towgood et al. (2009). We first ranked each of the 26 variables acquired from the 103 TD subjects, and then used the fifth scores from the top and from the bottom as the approximate 5 percentile cut-off criterion for each variable. Next, we applied this cut-off score to both TD and ASD group and identified the performances that were 'out-of range' (OoR). For any scores in each variable above the upper criterion were categorised as 'supra-normal' performance and for any scores in each variable below the lower criterion were categorised as 'sub-normal' performance. The number of subjects having 'supra-normal', 'intra-normal', and overall 'out-of-range' performances that combined both 'supra-normal' and 'sub-normal' performances in the TD and the ASD groups was summarised in Table 7.5. The statistical analysis to define significant between-group effects was examined by Fisher's exact test. Based on Towgood et al. (2009)'s result, hypothesised that the ASD group would have more OoR performance than the TD group, and a p=0.05 criterion was set for significance. Subjects with ASD were diagnosed with stereotyped mannerism and deficits on social interactions, and as a result, we hypothesised that the ASD group would demonstrate more ‘supra-normal’ performances on the variables measuring the repetitive behaviours, and show more ‘sub-normal’ performances on the variables measuring the ability requiring ToM.

Table 7.5. The result of the multiple case series approach analysis. The criterion for the range of typical performance was based on the top 5 and the bottom 5 scores of the TD group, which defined the boundaries of supra-normal and sub-normal performance applied to the ASD group. The number of ASD subjects showing OoR performance was the sum of the number of ASD subjects having both supra- and sub-normal performances.

PFC battery variable	Criterion for typicality		Number of ASD subjects with			Significance between group (p-value)[a]		
	bottom 5 scores	top 5 scores	sub-normal performance	supra-normal performance	OoR performance	sub-normal performance	supra-normal performance	OoR performance
The gambling test								
G_wrate	0.09	0.78	3	0	3			
G_lrate	0.15	0.93	1	1	2			
G_wrep	34.38	98.44	1	8	9		<0.001	0.003
G_lrep	29.69	93.75	4	6	10		0.009	0.001
G_wrt	811.5	2394.1	1	1	2			
G_lrt	714.1	3164.9	1	2	3			
The referenrial judgment test								
R_pscore	6	10	1	1	2			
R_wscore	7	12	1	0	1			
R_prt	881.8	3420.9	7	0	7	0.003		0.042
R_wrt	869.7	2622.4	9	1	10	<0.001		0.003
The video mentalizing test								
M_highacc	0.50	0.92	5	0	5	0.027		
M_lowacc	0.42	0.92	1	0	1			
M_highrt	7509.8	16097.4	7	1	8	0.003		0.01
M_lowrt	7161.4	15279.4	4	4	8			0.01
The cartoon faux pas test								
F_fpacc	0.59	0.94	3	2	5			

F_nfpacc	0.53	1.00	4	0	4
F_compacc	0.57	1.00	1	0	1
F_fprt	5141.8	14549.2	2	1	3
F_nfprt	4600.4	15865.8	2	1	3
F_comprt	4949.4	15895.6	2	1	3
F_dprime	0.65	3.50	2	0	2
F_beta	0.07	3.32	2	2	4

[a] the significance was calcuated using Fisher's Exact test (two-tailed)

In the gambling test, the result demonstrated that the ASD group had significantly more 'supra-normal' performance and 'OoR' performance than the TD group on the overall repetitiveness in the win and the loss conditions. No significant differences were found on the overall risk rate and the overall reaction times in both conditions. In the referential judgment test, the ASD group revealed significantly more 'sub-normal' performance and 'OoR' performance than the TD group on the overall reaction times in both personality and weight conditions. No significant group difference in the consistency score was found in either condition. In the video mentalizing test, the result showed the ASD group had significantly more 'intra-normal' performance on the accuracy for high-mentalizing videos, as well as significantly more 'intra-normal' and 'OoR' performance on the reaction time for high-mentalizing videos. For low-mentalizing videos, ASD subjects had significantly more 'OoR' reaction time than TD subjects, but no significant difference was found on the accuracy. In the cartoon faux pas test, no significant between group effects were found on any variables. However, it is important to note that the upper limit for the accuracy was 100%, which suggested a potential ceiling effect that prevented us identifying the 'supra-normal' performance on the faux pas detection ability. As a result, we compared the number of subjects having perfect performance (accuracy = 100%) in both groups, as the indicator for 'supra-normal' performance. Given that ASD subjects were people diagnosed with deficits on social behaviours, we hypothesised that the TD group would have significantly more 'supra-normal' performance than the ASD group. The result confirmed our hypothesis, which identified 28 of the 103 TD subjects scored 100% on the accuracy for non-faux pas cartoons, but only 3 of the 30 ASD subjects scored 100%, and this (p=0.027 in Fisher's Exact test, one-tailed).

We further analysed the pattern of performance across the four psychometric tests on the individual basis. When examining each ASD subject individually, not any ASD subjects had ‘supra-normal’ performances across all tests, nor did any ASD subjects have ‘sub-normal’ performances across all tests. Many ASD subjects demonstrated ‘supra-normal’ performance in some tests, and ‘sub-normal’ performance in others. To compare the average number of ‘OoR’ performance between groups, the result revealed that the ASD group had significantly more ‘OoR’ performance that the TD group (ASD mean=3.133; TD mean=1.291; $t(131)=4.830$, $p<0.001$). Furthermore, to compare this atypicality on the individual basis, we calculated the proportion of subjects within each group having at least one ‘OoR’ performance across the four tests. The results revealed that the ASD subjects had significantly higher atypicality than the TD group, where 27 out of the 30 ASD subjects, compared with 61 out of the 103 TD subjects, had at least one ‘OoR’ performance ($p=0.002$ in Fisher’s Exact test).

Binary logistic regression analysis

In binary logistic regression analysis, we included the experimental variables from the PFC battery as a predictor factor, and group membership (i.e., ASD=0, TD=1) as dependent variable. The variables included for binary logistic regression analysis were the same set of variables as included for the multiple-case series approach analysis, which were listed below: the overall risk rate, the overall repetitiveness, the overall reaction time in the win and loss conditions of the gambling test; the consistency score, the overall reaction time in the personality and the weight conditions of the referential judgment test; the accuracy and the reaction time for high-mentalizing and low-mentalizing videos of the video mentalizing test;

the accuracy, the reaction time for comprehension, faux pas, non-faux pas cartoons, as well as the d-prime and β values of the cartoon faux pas test. We further inputted the number of ‘OoR’ performance across the four tests acquired from the multiple case series approach as an additional predictor factor.

Backward stepwise model using Wald statistics as the criterion showed that the model explained 49.6% (Nagelkerke R square value) of the variance in the group factor. In addition, the goodness-of-fit test showed no mis-specification of the predictive capacity of the model (Hosmer and Lemeshow X^2=9.786, p=0.280). The classification table in the last step reveal that the model correctly predicted overall 87.2% of cases (ASD: 56.7%; TD: 96.1%), compared with the null model which predicted 77.4% (ASD: 0%; TD: 100%). The variables that survived the Wald statistics were the overall repetitiveness in the win condition of the gambling test, the overall reaction time in the weight condition of the referential judgment test, the reaction time for videos requiring high intentionality of the video mentalizing test, the reaction time for the comprehension cartoons of the cartoon faux pas test, and the number of ‘OoR’ performance of the PFC battery (see Table7.6).

Table 7.6. The PFC battery variables that survived from Wald statistics in a descending order, which showed significant predictive power for group membership.

	B	S.E.	Wald	Sig.	Exp(B)
number of OoR performance	-0.454	0.128	12.606	<0.001	0.635
G_wrep	-0.600	0.200	9.148	0.002	0.942
R_wrt	0.001	0.000	6.453	0.011	1.001
M_highrt	0.000	0.000	3.990	0.046	1.000
F_comprt	0.000	0.000	8.081	0.004	1.000

7.11 Discussion of the between-test analysis

The aim of this chapter is to examine the relationships of the variables between each test of the PFC battery. Based on previous related studies that focused on investigating the cognitive functions supported by the PFC region, we used a range of statistical analyses to examine these different, yet inter-correlating functions. We have discussed the potential explanation of the findings, and some preliminary speculations based on results observed in the current chapter.

<u>The effect of general intelligence to the PFC battery</u>

In a series of pathological studies comparing between-group differences including patients with frontal lobe lesions, Parkinson's disease, frontotemporal dementia, and schizophrenia (Roca et al., 2011, 2012, 2013, 2014), the results consistently showed that a *general* factor that accounted for some, but not all of the executive deficits identified in the compared pathological group. Specifically, in the Roca et al. studies, the significant between-group differences observed in some sets of executive function tests became insignificant after the effect of general intelligence was partialled out, but remained significant for some other executive function tests, including multi-tasking, social cognition, and risky decision-making tests. Amongst the PFC battery variables, Spearman rank-order correlation analysis demonstrated several significant relationships between the NART score and the variables showing significant group difference between the TD and the ASD groups. It is important to note that G_wrep was the only variable that showed significant between-group effect, as well showing significant correlation with the NART score in both groups. Other variables including G_wrt, G_lrt, M_highacc, F_nfpacc, and F_dprime were significantly correlated (all $p<0.05$) with the NART score only in the TD group, but not in the ASD group. This distinct correlation with the NART score between groups implied that general intelligence had more profound contribution to PFC battery variables that identified group differences to TD subjects than to ASD subjects. On the other hand, the null relationship between the PFC battery variables and the NART score in the ASD group suggested that the impaired performance could not be explained by a general factor that might potentially worsen the behaviours as a whole. Interestingly, the only variable that showed significant relationship with the NART score in both groups, the G_wrep, was evident to be higher in the ASD group, instead of showing deficits, compared with the ‘typical’ TD group performance. Further investigation is required to examine the link between general intelligence and the repetitiveness to risky actions, and test if the effect was similar to TD and ASD subjects. Next, ANCOVA model revealed that after partialling out the NART score, all the significant between-group differences remained. This indicates that the group differences observed in the current study cannot be explained by differences in crystallized intelligence. In the PFC battery used here, the identified deficits in accurately responding to high-mentalizing videos, non-faux pas cartoons, and lower sensitivity to faux pas detection in the ASD group could not be explained by a general factor, but may reflect the primacy of diagnosed social impairment in ASD subjects instead. Similarly, other significant between-group differences including higher overall repetitiveness in the win condition, general slowness across decision-making and social cognition domains, which were categorised as the core symptoms of ASD, could not be explained by general intelligence either. Together these results revealed that the observed difference between the ASD and the TD groups could not be explained by general intelligence.

Nevertheless, it is important to notice that the performance showing significant group difference in the ASD group did not significantly correlate with the NART score, except for the G_wrep variable. It is therefore possible that the ANCOVA approach used in Roca et al.'s series of studies is not a powerful tool to control for the mediating contribution that led to significant group difference, in this case, the estimated general intelligence measured by the NART score.

The effect of gender to the PFC battery

Previous psychological studies have identified gender-related differences on ToM-related and risky decision-making paradigms. Coincidently, ASD is a gender-linked developmental disorder with impairments on social behaviour, along with repetitive behaviours. Furthermore, previous structural-based analysis also found that the PFC region was one of the brain regions that showed sex-related differences, and that the PFC region is involved with a range of higher-level cognitions including ToM and gambling actions. Taken together, it is possible that there might have been an inter-relationship between gender (male vs. female), group (TD vs. ASD), and the regional volume in the PFC region. Repeated measures ANOVA was conducted to explore the group x gender interactions on the variables measuring risky decision-making and social interactions in the PFC battery.

In the gambling test, behavioural results showed that the overall risk rate found a significant group x gender x condition interaction on the overall repetitiveness, and the group x gender interaction was only significant in the loss condition. There were two possible implications to this finding. When examining the effect from the perspective of gender, the male ASD subjects made significantly more repetitive behaviours when facing potential losses than female ASD subjects did, but no significant gender effect was found in the TD group. This suggested an enhanced repetitive mannerism in the male ASD subjects compared with female ASD subjects, which suggested this repetitiveness as a male-like symptom, which is in line with the extreme male theory on autism proposed by Baron-Cohen (2002). When examining the effect from the perspective of group, male ASD subjects made significantly more repetitive behaviours when facing potential losses than female TD subjects did ($t(73)=2.171$, $p=0.033$), but no significant group effect was found in female subjects between the TD and the ASD groups ($t(56)=-1.365$, $p=0.201$). This selective enhanced repetitive mannerism of male ASD subjects further supports the extreme male theory on autism proposed by Baron-Cohen (2002). When considering the effect between the win and the loss conditions, De Martino et al. (2008) showed that both TD and ASD subjects demonstrated the framing effect (Tversky and Kahneman, 1981), where people tended to avoid risk in a positive frame but to seek risk in a negative frame. To investigate further this extreme male feature of repetitive behaviour rather than risk-taking behaviour in ASD subjects, we examined the framing effect on the overall repetitiveness amongst the ASD subjects. In male ASD subjects ($n=20$), a paired t test found no significant difference between the win and the loss condition ($t(19)=1.757$, $p=0.095$), but female ASD subjects ($n=10$) showed significantly higher repetitiveness to potential wins than to losses ($t(9)=3.319$, $p=0.009$). This indicated an insensitivity of frames in the repetitive behaviours specifically for male ASD subjects, which is in line with Lai et al. (2011), who demonstrated that ASD females had less autistic behaviours than ASD males in RSB (repetitive, restrictive and stereotyped behaviours) sub-scores in the ADOS

(Autism Diagnostic Observation Schedule; Lord et al., 2000). No significant gender- and group-related difference was found in the referential judgment test.

In the video mentalizing test, analysis of the accuracy revealed a significant main effect of group, where the ASD subjects made fewer correct responses to questions varying in appropriateness than the TD subjects. Repeated measures ANOVA showed a significant condition x group interaction, where the observed deficits in the ASD group in making correct decisions was only significant when answering high-mentalizing videos, but the group difference was not significant when answering low-mentalizing videos. This result was consistent with previous behavioural ASD studies showing ToM-related impairment using videos as stimuli (Heavey et al., 2000; Golan et al., 2006). In previous ToM studies measuring gender-related effects, Stiller and Dunbar (2007) used TD subjects and found that TD male subjects had lower capacity in perspective-taking than TD female subjects. Lai et al. (2011) used ASD subjects and showed that female ASD subjects had fewer socio-communication difficulties than male ASD subjects did. In the video mentalizing test, no significant gender-related effect or interaction was found. A possible explanation for this insignificant gender-related effect might come from the difference on the measurement between experimental paradigms. In Stiller and Dunbar (2007), written short stories were used as stimuli and the measurement was the ability to answer perspective-taking question (up to nine orders) until one started to fail. Importantly, the capacity of answering perspective-taking questions was correlated with the performance on memory questions, which suggested a potential mediating effect from memory-related ability to the measurement. In Lai et al. (2011), the socio-communication ability was measured by the diagnostic algorithm of natural interpersonal contact whilst assessing ASD syndromes, and this interview-based instrument on detecting ASD, a gender-linked syndrome, might not be an appropriate measure for detecting any gender-related effect. In the video mentalizing test, this lack of gender difference, along with a significant group x condition interaction, implied a selective impairment in responding to videos involving high intentionality regardless of the gender of the subjects. In the cartoon faux pas test, repeated measures ANOVA found a significant group effect showing that the ASD subjects made significantly fewer correct responses to the depicted social interactions in general. Although no significant group x condition was found, the ASD group had lower accuracy to all three kinds of depicted social scenarios, and the difference was highest to the non-faux pas cartoons (TD: 0.854; ASD: 0.767), compared with the faux pas cartoons (TD: 0.795; ASD: 0.751) and the comprehension cartoons (TD: 0.804; ASD: 0.790). This prominent yet not significant deficit in rejecting non-faux pas cartoons was consistent with the findings identified in Chpater6 introducing the cartoon faux pas test. The significant lower d-prime score in the ASD group compared with the TD group was also consistent with the finding shown in Chapter 6. These results together confirmed that the ASD subjects had impairments in distinguishing social scenarios with and without embarrassment, and manifested an over-detection to non-faux pas cartoons.

<u>The identified components in the PFC battery</u>

The PFC battery included four psychometric tests measuring a wide range of behaviours relating to different aspects of decision-making and social cognition domains. It is possible that some experimental variables, within or between tests, actually tapped overlapping cognitions, given that shared features between decision-making and social cognition have been proposed. In order to investigate how many uncorrelated variables, and further isolate the underlying factor in the

PFC battery, we conducted PCA of the TD and the ASD groups separately. In the first step of PCA, we focused on the within-test factor of each test in each group. In PCA, the first extracted component has the highest eigenvalue and explains the most variance. In the PFC battery, PCA of each test consistently identified reaction time as the first component. This converging evidence indicated a general factor of response speed across experimental conditions of each test. Apart from the reaction time factor, the within-test PCA highlighted several important implications within each test.

In the gambling test, PCA of the TD group identified the overall risk rate and the overall repetitiveness in both the win and the loss conditions as separate components. This further supported the view in chapter 3, which suggested that the risk rate and the repetitiveness variables measured two different aspects of risk-taking behaviours. Furthermore, orthogonal transformation in PCA did not differentiate between the risk rate and the repetitiveness under win and loss domains. Yet in the ASD group, the overall risk rate in the loss condition was extracted as a different component from the overall risk rate in the win condition, and was identified as the same component as the 'G_reactiontime' factor. This implied a possible relationship between the risk-taking behaviours to avoid potential losses, and the response latency to evaluate uncertain situations, amongst ASD subjects. This independence of the risk rate in the win and the loss conditions further suggested that the underlying mechanism to evaluate risk-taking actions to gains and losses was different in ASD subjects. Importantly, the overall repetitiveness in the win and the loss conditions were loaded upon the same component in the ASD group as well. This suggested that the level of repetitive behaviour to potential wins and losses was correlated with each other in both TD and ASD subjects.

In the referential judgment test, PCA identified the consistency score in the personality and the weight conditions as the same component in both groups. This result supported our speculation of the effect of our scoring scheme in chapter 4, where the calculation of the consistency score using Repertory Grid approach was unable to reflect the advantage of self-referential processing. Nevertheless, the behavioural result identified that subjects had distinct ranking scheme between conditions, and demonstrated significant effect of condition that differentiated referential judgments based on self-related constructs vs. self-unrelated constructs. A possible explanation of the PCA result was shown in the VBM regression analysis of the TD sub-group, where the consistency score was positively correlated with the GM volume in the right lateral OFC region in the weight condition and marginal significant in the personality condition. This suggested that the observed behaviour using the consistency score measured the ability to override previously established contingency of the internal metric as test progressed, a key feature required in performance of reversal-learning paradigm.

In the video mentalizing test, PCA of the TD subjects showed that the accuracies for the videos in three conditions (except for high-mentalizing dyad videos) were extracted as one single component. This may suggest that that the mentalizing process is a continuum, where videos requiring either high or low level of intentionality, as well as videos involving two, or more than two, characters required a shared resource but perhaps varied in degree of ToM-related ability. It is plausible that TD subjects implemented a certain amount of mentalizing ability to answer low-mentalizing videos. Castelli et al. (2000) asked subjects to passively view animations of geometric shapes moving in a way that simulated interactions amongst people, and observed increased activation in the medial PFC region. This medial PFC activation suggested that subjects projected their knowledge of social attributions even to life-less geometric shapes without ‘actual’ social interaction. In the video mentalizing test, subjects witnessed conversations in all kinds of videos, and naturally required perspective-taking ability to answer the questions afterwards. Since all the questions were identical (which statement best described the situation you have just seen?), this may have helped subjects to make decisions in a constant respond mode rather than being affected by emotional adjectives that might be suggested in the Awkward Moments Test or the RMF test (Heavey et al., 2000; Golan et al., 2006). In the ASD group, PCA identified that the accuracies for high-mentalizing videos and low-mentalizing videos were two orthogonal components. This highlighted an important implication that the ability to understand videos requiring high and low intentionality could be categorised by different psychometric components in the ASD group. In chapter 5 examining the effect of group, repeated measures ANOVA on accuracy demonstrated a marginal significant condition x group interaction, where a significant effect of group was only observed in high-mentalizing videos, but not in low-mentalizing videos. Nevertheless, when interpreting this marginal significant interaction from the perspective of condition, ASD subjects had significantly lower accuracy for high-mentalizing videos, compared with answering to low-mentalizing video, whereas TD subjects responded videos varying in intentionality in a comparable way. Together with the distinct PCA segregation between groups, these results provided another scope to explain the selective impairment observed in processing social situation requiring higher level of mentalizing ability, where ASD subjects responded to videos requiring high-mentalizing and low-mentalizing ability using different underlying mechanism, yet TD subjects considered videos varying in intentionality using the same cognitive process.

In the cartoon faux pas test, PCA of the TD group performances identified the accuracies for the faux pas and the comprehension cartoons as loaded on the same component, but the accuracy for the non-faux pas cartoons as a separate one. This suggested that the ability to correctly reject non-faux pas cartoons might rely upon a dissociable factor from correct identification of faux pas. In the ASD group, the accuracies for the faux pas and the non-faux pas cartoons were identified as supported by the same component, and the accuracy for the comprehension cartoons was a separate one. It is important to note that accuracies for the faux pas and the non-faux pas cartoons were in a negative direction. This negative correlation was in line with the implication from the signal detection analysis, where subjects implemented an internal response bias in faux pas detection, i.e., where the criterion became more conservative to yes responses, a better non-faux pas accuracy accompanied with a lower faux pas accuracy would be observed, and vice versa. To examine this negative correlation, Pearson's correlation analysis using the raw accuracy score provided the same pattern. The correlation between the accuracies for the faux pas and the non-faux pas cartoons was only significant in a negative way in the ASD group ($r=-0.395$, $p=0.030$), but not significant in the TD group ($r=-0.107$, $p=0.283$). This perhaps implied that only the ASD subjects implemented a certain internal criterion in faux pas detection when encountering questions asking if there was anything embarrassing, but the superior performances in the TD group on the non-faux pas accuracy was a standalone ability uncorrelated with the shift of response bias in a signal detection account.

The between-test PCA revealed that the underlying components in the PFC battery were distinct between the TD group and the ASD group. First, the factors relating to reaction time of each test were extracted as the component that explained most of the variance in both groups. Between-test PCA showed that, in the TD group, the G_reationtime, and the R_reactiontime factors were identified as one component, and the M_reactiontime, the F_reactiontime factors were extracted as another component. This separation of the factors relating to reaction time suggested a possible dissociation between the processing speed of the decision-making and social cognition domains amongst TD subjects. On the other hand, in the ASD group, the reactiontime factors in all the four tests were identified as the same component. This result suggested that ASD subjects who responded slowly in one test would also respond slowly in others, which indicated a universal response speed across psychometric tests measuring decision-making and social cognition domains. This difference on the reactiontime factors between groups implied that, in a set of tests measuring a range of functions supported by different PFC sub-regions, the response speed in ASD subjects across domains, mostly a general slowness, was more predictable. However, TD subjects demonstrated a specialisation of processing speed between decision-making and social cognition domains. In the TD group, the third component following the reactiontime factors in decision-making and social cognition domains included the G_repetitiveness, the M_high+lowmentalizing, and the F_nfp factors. The identification of the G_repetitiveness and the M_high+lowmentalizing factors as the same component was consistent with the VBM results reported in previous chapters. VBM regression analysis showed that mentalizing ability in the video mentalizing test and the overall repetitiveness in the gambling test were significantly correlated with similar GM cluster in the dorsomedial PFC region. PCA demonstrated converging evidence and further provided behavioural validation on the structural-based analysis using neuroimaging technique. As described in Chapter 2, evidence suggested by functional neuroimaging studies provided only indirect linkage between brain activation and the approximate brain region, and the ‘specificity’ issues of the meta-analysis approach.

The PFC battery established strong evidence on the function-structure relationship, where between-test PCA identified the orthogonal underlying components, and VBM localised a detailed PFC sub-region that linked to the cognitive behaviours across decision-making and social cognition domains.

The heterogeneity of the ASD subjects evident by the PFC battery

In order to investigate the unique functional specialisation amongst the ASD subjects, we conducted a multiple-case approach following the rationale demonstrated in Towgood et al. (2009). Compared with the psychometric tests administered in Towgood et al. (2009), which included measurements of language, perception, memory and executive functions, the PFC battery measured the cognitive functions supported by the PFC region evident from previous related fMRI studies. VBM results in previous chapters validated that the experimental variables we calculated were associated with different PFC sub-regions using a hypothesis-testing approach. Furthermore, it is important to note that Towgood et al. (2009) recruited only 21 ASDs and 22 matching TDs for the single case series approach analysis. It was reasonable to use smaller number of subjects given that the neuropsychometric tests they administered were already routinely used in clinical practice. In the current study, we used newly developed psychometric tests, and as a result, a distribution-free approach was conducted to set up the criterion based on the finding from 103 TD subjects to define the ‘atypical’ performance in the ASD group. In Towgood et al. (2009), the group-level analysis revealed only a limited set of deficits in the ASD group including processing speed, visual memory and executive functions involving inhibition, initiation and set shifting. In the current study, previous chapters demonstrated that the ASD subjects, compared with TD subjects, responded significantly slower in all the four tests, as well as significantly higher repetitiveness to wins in the gambling test, significantly lower accuracy for high-mentalizing videos in the video mentalizing test, and significantly lower accuracy for the non-faux pas cartoons. These results further revealed a profound group-level deficit in ToM-related abilities, which was not shown in Towgood et al. (2009).

In the single-case analysis conducted by Towgood et al. (2009), the variation of the wide range of functions was demonstrated by the combined 77 ‘measures’ from a huge set of tests in a neuropsychological battery. The atypical performance was therefore calculated by using two standard deviations of the standardised score as the criterion to highlight the atypical performance. In the current study, the OoR performance was defined by the best and the worst of five scores amongst TD subjects as our criterion for atypical performance. Then we conducted Fisher’s exact test to test the significance of any between-group effect using the number of subjects that showed atypical behaviours in each test. The results were consistent with the findings in Towgood et al. (2009), where the higher variation cannot be explained by a total impairment across a set of psychometric tests. Some ASD subjects were observed to have ‘supra-normal’ performance in one test but ‘sub-normal’ in another. Fisher’s exact test revealed that the proportion of subjects with ‘OoR’ performance was significantly higher on the G_wrep, the G_lrep, the R_prt, the R_wrt, the M_highacc, and the M_highrt in the ASD group than in the TD group. In previous PFC chapters, we showed that ASD subjects had significantly higher repetitiveness, significantly slower reaction time on referential judgment, significantly lower accuracy and slower reaction time than TD subjects in various aspects of decision-making and social cognition based on group-level analysis. Multiple case series approach further identified the ‘atypicality’ of the ASD subjects in repetitive mannerisms, response speed, and ToM-related ability, which were all diagnostic feature of ASD syndromes, based on a single-case approach. In the cartoon faux pas test, given that the upper limit exceeded a perfect score of 100% on the accuracy, we further examined the number of subjects who scored 100% in the cartoon faux pas test. Fisher's exact test revealed that the number of subjects who had perfect scores on the non-faux pas accuracy was significantly higher in the TD group than in the ASD group. This indicated that, when considering the behavioural data acquired from the 103 TD subjects as 'typical', the ASD group had fewer subjects supposing to have perfect correct rejection of potential faux pas. Compared with previous PFC battery chapter discussing the cartoon faux pas test, accuracy on the non-faux pas cartoons was also identified to be significantly lower in the ASD group than in the TD group. Multiple case series approach further confirmed this relative impairment of ASD subjects on social behaviour specifically to identify situations without social rule violation.

Comparing with the results reported in Towgood et al. (2009), the number of ASD subjects who had 'sub-normal' performance on response speed was significant higher on the R_prt, the R_wrt, and the M_highrt. This response slowness in decision-making and social cognition was consistent with the finding in Towgood et al. (2009), which showed deficits on measures of processing/motor speed. Interestingly, in the PFC battery, the multiple case series approach found that some ASD subjects, yet not the same subject, even had 'supra-normal' performance on reaction times across all four tests. This was another evidence of the marked variation within ASD subjects, and this unique heterogeneity was not apparent from the group-level analysis. When addressing the variation within individuals, ASD subjects had in average more number of 'OoR' performance than TD subjects did, and the proportion of subjects who had at least one 'OoR' performance was significantly higher in the ASD group than in the TD group. This individual-based result supported the results reported in Towgood et al. (2009), and further provided insights on the variation within the ASD subjects was also more prominent than the TD subjects, even using a set of newly developed tests measuring higher-level functions supported by the PFC region. Despite the results revealed in single-case analysis were mostly consistent with the group-level analysis of the PFC battery, the theoretical implication behind them is quite different. There are several possibilities that could lead to a significant difference using group-level analysis, e.g., the effect between members on the same direction, on mixed directions, or because of some extreme outliers. The multiple case series approach provided supporting evidence on the third possibility that the observed group differences was contributed by the 'supra-normal', or 'sub-normal' performance observed in the ASD group. When excluding all the 'OoR' performance in both groups, independent t tests revealed that only 4 out the 9 variables remained significant, which included the G_wrt, the G_lrt, the M_highacc, and the F_dprime factors. The five variables including G_wrep, the R_prt, the R_wrt, the M_highrt, and the F_nfpacc became insignificant when using group-level analysis (see Table7.7). However, the comparison of β values in the cartoon faux pas test became significant when excluding the 'OoR' performances, which was consistent with the result we discussed previously in chapter 6 regarding the exclusion of the unique cases in the ASD group. Hence, the danger of this possible averaging artefact (Shallice and Evans, 1978) explained the findings acquired at the group-level, which cannot display the true nature of the heterogeneity of a single member, especially for ASD subjects who were evident to have distinct functional specialisation within and between individuals (Towgood et al., 2009; Gilbert et al., 2009). This unique way of addressing the considerable variability between and within ASD subjects also provides a strong explanation for the mixed findings in the ASD literature using a range of psychometric paradigms between different researchers. Furthermore, one might suspect that ASD subjects demonstrated mostly impaired performance except for the repetitiveness in the gambling test, it is therefore possible that the identified 'higher variability' could be heavily relied on 'sub-normal' performance using the single case approach. In order to examine this possibility, we calculated the largest discrepancy in performance between all the PFC battery variables included for the multiple case series approach. For instance, if a subject scored Z=3 on one variable (where positive values indicated supra-normal performance) and Z=-2 on another (where negative values referred to sub-normal performance), then the subject got a range of score Z=5. Independent t test of this range of Z score between group revealed a significant difference (ASD mean=4.083, TD mean=3.384; t(131)=3.041, p=0.003), where the ASD group had significantly larger range of Z score than the TD group. This confirmed the higher variability we observed using single-case approach could not be solely explained by poor performance amongst ASD subjects, but demonstrated a greater functional heterogeneity in a range of cognitive functions supported by the PFC region. Furthermore, a robust and repeated finding regarding to variability between individuals proposed that males have a greater range of ability than females, and previous studies identified that men did fall at the extremes of the spectrum (Machin and Pekkarinen, 2008; Johnson, Carothers, & Deary, 2008). In the current study, independent t test on the range of Z score found no significant effect of group (male mean=3.613, female=3.449; t(131)=0.824, p=0.411), neither as group x gender interaction (F(1,129)=0.589, p=0.444). This null effect of gender suggested that the observed pattern of increased variability amongst ASD subjects was not an exaggeration of the 'typical' pattern of the enhanced gender-linked or male-like to be specific, variability. ASD is a male dominant developmental disorder and it was proposed that ASD could be considered as extreme of the normal male (see Baron-Cohen, 2002). Our result did not support this extreme male brain theory of ASD, and reflected an atypical functional specialisation within the ASC population instead.

Table 7.7. The change of significance (highlighted using v) to the main effect of group when i*ncluding* all cases and *excluding* OoR scores of the PFC battery variables using multiple case series approach.

	Effect of group *including* all cases (p-value)	Effect of group *excluding* OoR scores (p-value)	Effect of group: remained significant in both approaches	Effect of group: significance disappeared	Effect of group: significance appeared
The gambling test					
G_wrate	0.341	0.619			
G_lrate	0.864	0.749			
G_wrep	0.017	0.310		**v**	
G_lrep	0.436	0.499			
G_wrt	0.007	0.001	**v**		
G_lrt	0.035	0.002	**v**		
The referenrial judgment test					
R_pscore	0.390	0.226			
R_wscore	0.670	0.628			
R_prt	0.002	0.134		**v**	
R_wrt	0.001	0.128		**v**	
The video mentalizing test					
M_highacc	0.001	0.012	**v**		
M_lowacc	0.226	0.558			
M_highrt	0.017	0.509		**v**	
M_lowrt	0.465	0.483			
The cartoon faux pas test					
F_fpacc	0.154	0.239			
F_nfpacc	0.013	0.099		**v**	
F_compacc	0.428	0.542			
F_fprt	0.274	0.342			
F_nfprt	0.235	0.334			

F_comprt	0.712	0.963		
F_dprime	0.003	0.011	**v**	
F_beta	0.273	0.045		**v**

Several theories have discussed possible explanations for this higher functional heterogeneity observed in ASD subjects, for example, Minshew, Goldstein, & Siegel (1997) proposed that ASD is a disorder of complex information processing that leads to multiple deficits observed in different ASD cases. Geurts et al. (2009) raised similar explanations by hypothesising a frequent lapse of attention or arousal. In that case, a fluctuation on the reaction time within and between tests should be observed in the PFC battery indexed by sub-normal performance on variables measuring response speed. However, the results reported in this chapter did not fully support this hypothesis regarding attentional deficits in ASD subjects. For example, behavioural analysis of the gambling test found that the ASD group, compared with the TD group, showed higher acceleration of response speed in the later stage of the loss condition. At the between-test level, despite PCA revealing a robust general slowness in the ASD group across all four psychometric tests in comparison to the TD group, multiple case series analysis was able to highlight that some ASD subjects had supra-normal performances on reaction times. These results proposed that ASD subjects were able to 'catch up' or sometimes demonstrated 'enhanced' performance on psychometric tests measuring higher-level cognition. Another explanation for simultaneous supra-normal and sub-normal performance at a single-case level was introduced by Frith (2003). Frith (2003) speculated that the abnormalities in ASD subjects could result from reduced synaptic pruning in early years. This was evident from the robust observation of greater total brain volume in structural studies, where individuals with ASD had greater size and weight in post-mortem brains (Bailey et al., 1998) and greater brain volumes (Hardan et al., 2001). Critically, this abnormality of volumetric difference was not seen at birth (Courchesne et al., 2001) but manifested with an abnormally rapid rate of brain growth during infancy and slowed again during adolescence.

Brain growth accompanied by synaptic pruning is critical for cognitive development, where a major reorganisation of connectivity in the brain coincides with new formation of synapses, dendritic growth and myelination. The concept of pruning focuses on elimination of a large number of synapses to enable functional specialisation to facilitate cognitive processes (Huttenlocher, 1999). Previous functional neuroimaging experiments using executive function tests have demonstrated unusual functional specialisation by localising different peak activations between ASD and control groups (Gilbert, Bird, Brindley, Frith, & Burgess, 2008). Similarly, Gilbert et al., (2009) implemented an executive test that involved medial PFC activation and reported abnormal connectivity within the medial PFC region amongst ASD subjects. It is important to note that the results were analysed on a case-by-case basis, which clearly demonstrated that distinct brain networks were specialised for particular functions and hence resulted in highly diverse performance on the measured cognitive ability. This single-case approach using neuroimaging technique, along with the behavioural evidence reported in Towgood et al. (2009), supports an explanation based on a possible abnormality of synaptic pruning in a developmental perspective.

Potential diagnostic tools for identifying ASD in the PFC battery

After establishing the function-structure relationship in the PFC region, and further identifying the uniqueness of ASD subjects using group-level and single-case analyses, it is perhaps more clinically important to investigate the validity of the variables measured in the PFC battery to distinguish ASD from TD adults. In order to achieve this, we conducted binary logistic regression analysis that enabled us to find the variables that predicted group membership. A backward stepwise approach identified the number of OoR performances, as well as four variables from each of the PFC battery test including the G_wrep, the R_wrt, the M_highrt, and the F_comprt. The regression model showed that the number of OoR performance identified by the multiple case series approach highlighted the importance of the functional heterogeneity in the ASD population. As mentioned in previous sections, inconsistent findings were frequently reported in ASD studies, and probably the only consensus was the high variation of performance in different psychometric paradigms. It is therefore a possibility that the core feature of the ASD syndrome is remarkable individual uniqueness, which is evident by single-case analysis, and supports the synaptic pruning hypothesis (Frith, 2003). Next the regression model identified the G_wrep variable as having the second highest significance to survive the Wald statistics. This was consistent with the results demonstrated in the group-level, as well as the single-case approach analyses, and further confirms that this item-based variable measuring the response pattern to risky options provides a dissociable index of risk-taking behaviours other than risk rate, which is able to capture the core feature of the repetitiveness syndrome in ASD adults.

The remaining variables that survived Wald statistics criterion were the R_wrt, the M_highrt, and the F_comprt variables. It is interesting to see that all the remaining three variables were measurements of response speed in a particular experimental condition. In the referential judgment test, overall reaction time in the weight condition was able to predict group membership. Although significantly slower reaction times in ASD subjects was found in both conditions using group-level and single-case analyses, the overall reaction times in the personality condition was not identified as a good predictor for group membership. Indeed, the variance of the overall reaction times between groups was significant in the weight condition (Levene test of homogeneity of variance=9.681, p=0.002) but not significant in the personality condition (Levene test of homogeneity of variance=3.637, p=0.059). This indicates that the distribution of the overall reaction times in the weight condition was more clustered in the TD group (SD=556.71 msec.) than in the ASD group (S.D.=777.67 msec.), and as a result improved the predictability of group membership. Nevertheless, the Levene test of homogeneity variance was not significant between groups in all the other four variables that predict group membership (number of OoR performance: p=0.074; G_wrep: p=0.738; M_Highrt: p=0.129; F_Comprt: p=0.768). This indicates that the predictive power of the other variables could not be explained by the distribution of data. In the video mentalizing test, only the reaction time for high-mentalizing videos was a significant predictor of group membership. The accuracy for high-mentalizing videos, despite a significant group difference found at both group-level and single-case level analyses, did not survived the Wald statistics. A possible explanation was provided by PCA, where the response speed was identified as the first component in the video mentalizing test that explained the most variance amongst all other variables. After partialing out the covariance between variables, the stepwise method revealed the reaction time for high-mentalizing videos that had the strongest, as well as isolated predictive power for group membership. Lastly, the reaction times for the comprehension cartoons in the cartoon faux pas test were identified as a good predictor for group membership. It is quite puzzling to find this variable has significant predictive power given that both group-level and single-case analyses found no significant group effect. However, between-test PCA found that ASD subjects had the reactiontime factors across four tests as the same component, whereas TD subjects had the reactiontime factors in decision-making and social cognition domains separately. It is possible that the reactiontime factors in each test were strong candidates for predicting group membership, and the reaction time for the comprehension cartoons in the cartoon faux pas test was the most representative one that independently differentiated between the TD and the ASD groups. In other words, the significant predictive power on the F_comprt was a product of the distinct between-test PCA result on the reaction time-related factors.

Chapter 8. PFC region and prospective memory

8.1 Theories of human prospective memory studies

In previous chapters, we discussed the functional role that different PFC sub-regions play in higher-level human cognition in decision-making and social cognition. It is widely accepted that the PFC region supports executive function (EF), an umbrella term that covers top-down regulatory processes (Alvarez and Emory, 2006). These executive processes contribute to a range of cognitions that are essential not only for previously learnt or stored information (e.g., decision-making and social cognition), but also for foresight of future events. The ability involving remembering to execute a future intention is referred as prospective memory (PM). Such ability is essential for facilitating simple tasks like remembering to reply to emails, as well as critical situations like remembering to perform safety checks before a flight takes off. Previous evidence has established a relationship between PM ability and the PFC region by demonstrating ‘acquired’ PM deficits in patients with structural abnormality in the PFC region (Fortin, Godbout, & Braum, 2003; Volle, Gonen-Yaacovi, de Lacy Costello, Gilbert, & Burgess, 2011). Previous studies examining PM focused on investigating the linkage between PM capability and executive processing by using different kinds of neuropsychological tests (Kliegal, Eschen, & Thone-Otto, 2004; Knight, Titov, & Crawford, 2006; Marsh & Hicks, 1998; McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999). It has been claimed that prospective memory is a complex function that involves many theoretically independent cognitive processes including planning, sustained attention, inhibition, multi-tasking, and even retrospective memory (RM). These underlying processes have been shown to associate with different PFC sub-regions, and impairment during any of these processes might result in observable deficits in PM. Therefore, although converging evidence from lesion and behavioural studies has established the essential role of the PFC region played in PM, it seems possible to suspect that distinct neural processes supported by different PFC sub-regions contribute to different aspects of this complex function.

Earlier evidence discussing PM function, or PM-like deficits to be precise, came from a classic single case study reported by Eslinger and Damasio (1985). The patient EVR, who had undergone surgical removal of bilateral frontal meningioma, was once a financial officer and a respected member of his community. After the surgery, EVR lost his job, bankrupt, was divorced by his wife, and accompanied with a serious of inappropriate actions. Critically, extensive psychological evaluation found no deficit, where EVR was diagnosed with above average IQ and unimpaired performance on EF test like the Wisconsin Card Sorting test, and still able to discuss professional matter relating to work and moral decisions. Nevertheless, EVR was unable to make simple daily decisions like which to buy, where to eat, what to wear, and often ended up with making no decisions at all. These symptoms showing disorganisation of daily events were similar to PM problems, and highlighted an important implication that individuals with normal intelligence and intact performance on some executive functions tests might show some selective executive dysfunctions similar to PM impairments. Nevertheless, no qualitative assessment or laboratory-based tests were developed to specifically examine PM-related performances at that time, which limited the implications of the EVR case to prospective memory. Later, Shallice and Burgess (1991) reported three patients suffering frontal lobe damage following traumatic brain injuries. Similarly, these three patients had normal intelligence and intact performance in a range of EF tests, but selectively impaired on the Multiple Errands Test (MET) and the Six

Element Test (SET) developed by Shallice and Burgess (1991). For example, these patients demonstrated many kinds of erroneous behaviours in SET and MET that could be interpreted as PM failures. Goldstein, Bernard, Fenwick, Burgess, and McNeil (1993) further confirmed the dissociable PM-related deficits from the EF tests by reporting a clinical case of GN, who had a resection of left frontal pole region and subsequently showed disorganised behaviours in his daily life. Despite normal cognitive abilities with normal intelligence, GN made significantly more errors than controls in the MET (Shallice and Burgess, 1991). These PM lesion case studies highlighted the distinction between PM deficits and patients with executive dysfunctions, where PM-specific deficits could not be identified by neuropsychological paradigms sensitive to EF impairments.

In order to dissociate PM, or even PM-specific deficits if any, Burgess, Veitch, Costello, & Shallice (2000) recruited patients with brain lesions showing strategy application disorder and gave a multi-tasking procedure to investigate the contributions of task learning and remembering. Anatomical-behavioural analysis identified that different stages of multitasking seemed to be disrupted by lesions to different brain regions. Critically, structural equation modelling revealed three underlying constructs that supported multitasking: retrospective memory, prospective memory, and planning. It was shown that the left anterior and posterior cingulate cortices played an important role in retrospective memory, whilst the prospective memory and planning components required cognitive processes supported by the left BA 8, 9 and 10 and the right dorsolateral PFC region. This result further suggested that the components supported by the PFC region not only contribute to PM performance, but also contributed to other behaviours. The advance of neuroimaging techniques provided another approach that enabled us to examine the link between the PFC region and PM ability directly. Burgess, Quayle, and Frith (2001) used positron emission tomography (PET) technique to investigate the brain activity associated with PM performance, and found that regional cerebral blood flow (rCBF) increased in the lateral BA10 region in PM conditions relative to 'baseline' task alone. Incidentally, Okuda et al. (1998) also reported increased brain activity in the frontal polar region, but the experimental design in Okuda et al. (1998) did not provide enough evidence to determine if the observed PFC activation was associated with intention maintenance, an essential factor relative to PM, or simply reflected involvement for divided attention between planned or routine actions. On the other hand, in Burgess et al. (2001), increased rCBF in the lateral BA10 was discovered in the condition where subjects were told that a PM target might appear, but none actually did. This validated the role of the lateral BA10 in the maintenance of a delayed intention rather than simply cue recognition or intention execution. Furthermore, another PET study conducted by Burgess, Scott, & Frith (2003) revealed that the medial BA10 was more active in 'baseline' condition than in PM condition. These two PET studies (Burgess et al., 2001; 2003) established a standard pattern of brain activations within rostral PFC region for the PM paradigm.

With the increasing amount of research discussing PM functions, a variation of PM tests were developed to focus on examining different factors that affected PM performance. Theories and ideas often originated from functions that were intensively studied in the past. For example, the phenomenon relating to the acquisition and the reproduction of existing information or content is referred as retrospective memory (RM; Baddeley & Wilkins, 1984). In RM experiments, subjects are typically asked to learn and remember certain experimental material during an encoding stage, and subsequently are required to remember the learnt materials at the appropriate time, or a retrieval stage. Despite the opposite direction along the temporal scale, where RM investigates mental processes related to the past, and

PM examines the cognitions relating to the future, it is unsurprising that PM and RM shared a similar neural machinery since a growing body of literature demonstrates that imagining the future depends heavily on remembering the past (see Schacter, Addis, & Buckner, 2007 for review). In the encoding stage of PM studies, subjects are required to remember to perform a delayed intention in the future. Subsequently, in the retrieval stage, subjects are required to maintain the delayed intention and execute the associated actions depending on the context. A common distinction between the types of context involving PM intentions was event-based and time-based PM (Einstein & McDaniel, 1990; Park, Hertzog, Kidder, Morrell, & Mayhorn, 1997). In event-based PM, the environment provides external cues to prompt the encoded intention, whereas in time-based PM, the intention was encoded and expects to be executed either at a specific time or after a specific period since the delay elapsed. For the purpose of simulating a real-life PM situation, the experimental paradigm of PM consists of an ongoing (OG) activity (Ellis, Kvavilashvili, & Milne, 1999) in order to prevent continuous, conscious rehearsal of the encoded intention during the entire delay period. Later, PM instructions are introduced and subjects are asked to remember to perform an additional action under a particular circumstance, or in a particular retrieval context (Ellis, Kvavilashvili, & Milne, 1999). As a result, a typical PM paradigm allows measuring performance including the proportion of correct responses, as well as reaction time, for the PM task and the ongoing task. Burgess, Scott, & Frith (2003) summarised the characteristics of laboratory-based PM studies, and different kinds of manipulations were implicated including the cognitive load of the ongoing task, the nature of the PM task, the material used for the task, the relationships between encoding and retrieval, in order to examine different cognitive processes relating to PM.

Different theories have been proposed to explain the underlying processes supporting PM ability. In PM experiments, one of the most debatable issues was the mechanism that supports successful PM detection. Smith (2003; Smith & Bayen, 2004) proposed a preparatory attentional and memory processes (PAM) theory, which proposed that PM retrieval was based on a capacity-demanding process, and an attentional mechanism was involved in monitoring the environment. As a result, successful event-based PM required maintaining a preparatory state to monitor the occurrence of PM target events. The critical notion of the PAM theory is that limited cognitive resources are allocated between the ongoing activity and preparation for the detection of PM targets. In order to enable this constant discrimination between PM-related and PM-unrelated events, the PAM theory also highlighted the engagement of RM processes in PM tasks, where recollection of the intended action was likely to occupy some limited attentional resources. Supporting evidence for the PAM theory came from the intention ‘cost’ of resources available for the ongoing task, where response speed for the ongoing task before PM instruction was faster than response speed for the ongoing task after PM instruction. This intention cost was robust even when the expected PM cues were not actually presented at all (Burgess et al., 2001; Smith, 2003). Similarly, other PM studies yielded consistent findings on the role of preparatory attention in PM (Burgess, Quayle, and Frith, 2001; Gilbert, Gollwitzer, Cohen, Burgess, & Oettingen, 2009; Marsh, Hicks, & Cook, 2005; Marsh, Hicks, & Cook, 2006). However, this constant use of attentional resources might be possible only in laboratory-based experiment. In other words, such demanding functioning of attentional resources was not possible for real-life situations (McDaniel and Einstein, 2007). Therefore, McDaniel and Einstein proposed a spontaneous retrieval theory based on the feedback from their subjects whilst administering their PM experiments. It was reported that some successful PM detection popped into subject's minds without any attentional processing (McDaniel, Robinson-Riegler, and Einstein, 1998). This spontaneous detection of PM intentions was linked to the automatic-associative mechanism proposed by Moscovitch (1994), who described that an associative link was formed between the intention and the action. If the PM cue produced sufficient power to activate the memory trace, then the associated action would be transferred to awareness without too much effort (McDaniel, Robinson-Riegler, & Einstein, 1998). In order to coincide with the contradictory PAM theory and the robust evidence consistent with the PAM theory, McDaniel and Einstein (2000) updated their single-process spontaneous retrieval theory to a multi-process theory. The idea of the multi-process theory was to account for both attention-demanding monitoring and spontaneous processes during successful PM retrieval. To decide which approach would be more dominant, the experimental material used in the PM and the ongoing tasks, as well as different manipulations, were likely to favour each process. For example, the extent of attention directed from the ongoing activity to the PM cues (McDaniel and Einstein, 2007), cognitive load of the ongoing activity (March, Hancock, and Hicks, 2002), saliency of the PM cue (McDaniel and Einstein, 2000), association between the PM cue and the intended action (McDaniel, Guynn, Einstein, & Breneiser, 2004), importance of the PM intention (McDaniel and Einstein, 2000), the length of PM retention interval (McDaniel and Einstein, 2007), and even the planning process for PM intention (Burgess, Dumontheil, Gilbert, Okuda, Scholvinck, & Simons, 2008). Therefore, it seemed necessary to investigate the complex cognitive processes that contribute to this flexible and inter-dependent mechanism in PM proposed by McDaniel and Einstein (2000).

In the multi-process theory, one of the most critical factors that favouring spontaneous retrieval is the overlap between the delayed intention at encoding and the subsequent PM target in PM task. Based on the multi-process theory, the PM cue in the word condition and the PM cue in the syllable condition were referred to as the focal and nonfocal cues respectively. Focal cues were the kind of PM cues that overlapped with the information relevant to the ongoing task, and could rely on spontaneous retrieval processes. On the other hand, nonfocal cues were the kind of PM cues that were not part of the information relevant to the ongoing activity, and as a result required attentional monitoring to the environment. In Einstein et al. (2005), subjects were asked to do a category verification task as the ongoing activity, and then informed the PM instruction to respond differently when encountering a specific word (e.g., the word 'dormitory') or any word containing a specific syllable (e.g., the syllable 'tor'). The accuracy for PM cue detection was significantly higher for a specific word than for a specific syllable, and task interference to the ongoing activity, which was calculated by the difference of reaction time relative to the PM task, was found to be significant in the syllable condition but not in the word condition. This was interpreted as the contribution of focal processing, where the ongoing task encouraged processing of the features that were emphasised at encoding. As a result, this highlighted the importance of the focality on PM cues in subsequent PM studies (Brewer, Knight, Marsh, & Unsworth, 2010; Scullin, McDaniel & Einstein, 2010; Scullin, McDaniel, Shelton, & Lee, 2010). However, the contribution of the focality factor to PM performance has not yet been fully explored.

A cardinal distinction between the focality between PM cues was the varying level of specificity. In previous PM studies investigating the focality factor, focal PM cues were more specific (e.g., the word 'cat', the word 'tortoise', words with three e's), and non-focal PM targets were less specific (e.g., items from the 'animal' category, the syllable 'tor') (see Table.2 in Einstein and McDaniel, 2005; and also Meier and Graf, 2000). One might suspect that focal PM cues not only had higher specificity but also accompanied a higher degree of repetitive features between each other, compared with non-focal PM target. In other words, if a focal PM cue ‘tortoise’ was encoded, that was all the combined features in an exact order (e.g., t-o-r-t-o-i-s-e) that a subject needed to identify during PM retrieval. On the other hand, if a non-focal PM cue ‘tor’ was encoded, the PM targets could be flanked by additional letters (e.g., tor-ch, tor-pedo, tor-nado), which shared a lower degree of repetitive features, along with higher variations between potential PM targets. As a result, the difference between focal and non-focal PM cues might be a quantitative distinction between the repetitive features during encoding and a subsequent detection process. Coincidently, this repetitive exposure at the perceptual level using identical stimuli in focal PM cues was similar to the classic repetition priming effect, where the stimulus that was previously experienced leads to quicker and better performance for the later exposure of the same stimulus (Forster & Davis, 1984). This repetitive priming effect is more salient when the two stimuli are in the same modality, and was very robust when using perceptual, semantic, or conceptual materials (Biederman & Cooper, 1992; Friederici, Steinhauer, & Frisch, 1999). This posited a possibility that the advantage of focal processing, at least in certain degree, relied on repetition priming based on repetitive exposure to the identical features between encoding and retrieval in PM paradigm.

Another important feature between the level of focality between PM cues was the concept taken from the transfer appropriate processing (TAP), which was originally identified in RM experiments. The TAP effect indicated that memory performance could be influenced by the relationship between the way of information initially encoded and later retrieved (Morris, Bransford, & Franks, 1977). In order to examine the effect of TAP in PM paradigm, Meier and Graf (2000) asked subjects to perform the ongoing task requiring either semantic or perceptual processing to words, and the PM task required either semantic or perceptual processing to words. The result showed that performance was higher when the processing between ongoing and PM tasks were the same (i.e., semantic-semantic, perceptual-perceptual) than the processing were different. A series of studies were conducted to investigate the different contributions between TAP and transfer inappropriate processing (TIP) conditions to the level of the attentional demands required for successful PM performance (Marsh, Hicks, & Cook, 2005; Meiser and Schult, 2008; Abney, McBride, & Petrella, 2013). The converging evidence revealed that the degree of overlap between the experimental materials used during the ongoing task and the subsequent PM task influenced PM performances. As a result, combined with the implication from repetitive priming and the TAP effect, it is possible that the more specific a focal PM cue, the more perceptual similarity is shared between potential PM targets, which allows subjects to rely more on perceptual processing, compared with less specific non-focal PM targets. The bias between the reliance of perceptual processing might explain at least part of the link of the TAP effect observed in PM studies. In order to understand better successful PM detection, it seems necessary to dissociate the underlying mechanism of processing PM cues varying in focality under the situation where the effects of TAP and repetitive priming are controlled.

In the current PM experiment, we implemented three manipulations to control for the potential TAP and repetitive priming effects, and investigated the performance to PM cues varying in specificity:

(1) First, we used a cross-modal design to control for the effect of TAP to PM performance. To achieve this, the way that the PM target was initially encoded and later retrieved was in different format, e.g., the PM intention was encoded in

one format (e.g., verbal) and was the cue would be presented in the opposite format (e.g., non-verbal), and vice versa. It is important to note that, in previous PM studies investigating the TAP effect in prospective memory (Meier and Graf, 2000; Marsh, Hicks, & Cook, 2005; Meiser and Schult, 2008; Abney, McBride, & Petrella, 2013), the experimental material used were word stimuli. Despite labelling the semantic and perceptual conditions, subjects were required to focus more on the semantic features or the perceptual features of the word stimuli, instead of actually requiring processing of verbal vs. non-verbal materials. In the current PM experiment, the cross-modality design enabled us to control for the TAP effect, and provided direct measurement of the difference between processing PM intentions in verbal and non-verbal formats.

(2) Second, in order to control for a possible repetition priming effect when processing focal PM cues, we implemented an additional task during the PM encoding stage. Subjects were required to work out the PM intention by themselves instead of being orally or visually instructed as in a typical PM paradigm. To achieve this, subjects needed to decide which item was the ‘odd one out’ amongst three items (for example, a strawberry, a watermelon, and a briefcase), where two items belonged to the same category (e.g., a strawberry and a watermelon could be categorised as ‘fruit’), and the third item belonged to another category (e.g., a briefcase). By working out which was the ‘odd one out’, we ensured that participants could either come up with a specific PM target (e.g., a briefcase), and encode it as an ‘exemplar’ PM target, or alternatively, they could come up with a category (e.g., fruit), and encode it as a ‘category’ PM target. For example, for an ‘exemplar’ PM target (e.g., a *picture* of a briefcase)

might be encoded as the PM target. In the subsequent PM task, the PM target would be presented in the opposite format (e.g., the *word* ‘briefcase’). This was similar to the concept of focal PM cues proposed by the multi-process theory, except for the cross-modality design. On the other hand, for a ‘category’ PM target (e.g., a word ‘strawberry’ and a word ‘watermelon’ would make a category of ‘fruit’) would be encoded as the PM target. In the subsequent PM task, the item that belonged to the ‘fruit’ category (e.g., a picture of an apple) would be the PM target in the subsequent PM task. This category PM target example was similar to the concept of non-focal PM cue proposed in the multi-process theory, except for the cross-modality design. More importantly, through the ‘odd one out’ procedure, both the ‘exemplar’ and ‘category’ PM targets that subjects were required to detect during the subsequent PM task were self-generated in some senses, rather than presented perceptually or instructed orally in advance. This additional ‘odd one out’ procedure, as a result, controls the repetition priming effect at the perceptual level. Together with the cross-modality design, the comparison between ‘exemplar’ and ‘category’ PM targets therefore allowed direct measurement of the underlying mechanism for processing PM targets varying in specificity when the TAP and repetition priming effects to PM performance were controlled.

(3) Third, we used a design that enabled us to investigate the effect of target specificity without the potential confound of number of PM cues that may have occurred in previous PM studies. The prospective memory literature suggests that the number of PM targets has a profound impact on detecting PM targets that vary in specificity. For example, Marsh, Hicks, Cook, Hansen, & Pallos (2003) showed reduced PM accuracy when the PM intention was to execute the

PM action whenever any words of a semantic category were encountered (while performing an ongoing task) compared to where the PM intention was to respond to a specific word. This indicates the importance of cue quality including decreased cue specificity or increased number of cues upon PM accuracy. Furthermore, Knight, Meeks, Marsh, Cook, Brewer, & Hicks (2011) demonstrated that PM intentions associated with a specific target had higher level of intention-induced interference than PM intentions associated with a category intention. This indicates that specific PM targets have a higher chance to elicit a spontaneous response, and is consistent with the multi-process theory (Schullin, Einstein, & McDaniel, 2009). Recently, Wesslein, Rummel, & Boywitt (2014) investigated the effect of cue specificity and list length of PM cue to PM performance using multinominal model analysis. The results revealed that manipulation to list length of PM cue affects the distinction between the PM cue and ongoing items, as well as intention retrieval. By contrast, manipulation to cue specificity selectively affected intention retrieval only. This finding demonstrates that, although both manipulations resulted in decrements to PM performance, the effect of memory load and PM target specificity modulates different underlying cognitive processes. In the current PM experiment, in order to examine the effect of PM cues specificity more directly, we used block design where only one PM target was embedded in each block. This single PM target design therefore enabled us to investigate the effect of target specificity without other potential confound (e.g., the number of PM cues) shown in previous PM studies (Marsh et al., 2003; Wesslein et al., 2014). Although the cue specificity and number of cues might affect different underlying processes, this single PM target block design is especially important since subjects might gradually rely more on the repetitive features in focal processing conditions, where the same specific target appears multiple times throughout the test. Alternatively, category-type PM targets have a lower degree of repetitive features between each other, and therefore might elicit different effects unless this aspect of repetition is controlled for. .

The aim of the current PM experiment was to investigate the performance to PM targets varying in specificity. Previous PM studies revealed an advantage for processing focal PM targets (Einstein et al., 2005; Brewer, Knight, Marsh, & Unsworth, 2010; Scullin, McDaniel & Einstein, 2010; Scullin, McDaniel, Shelton, & Lee, 2010). Using the three manipulations described above, we controlled for the TAP and repetitive priming effects, and compared the performance between the 'exemplar' and the 'category' conditions, which are similar to the design of typical "focal" vs. "non-focal" PM conditions respectively. In the behavioural part of the study, based on the multi-process theory, we hypothesised that accuracy would be higher for detecting exemplar PM targets than category PM targets. For analysis of reaction time, we calculated the 'cost' of the response speed during the PM task, in relative to speed during the ongoing task. Based on the multi-process theory (Einstein et al., 2005), we hypothesised that the 'cost' of reaction time between ongoing and PM tasks should be significant in the 'category' condition, but not the 'exemplar' condition. Furthermore, a critical manipulation in the current PM experiment was the cross-modality design, where experimental materials could be in either word or picture format. There is a robust psychology effect that concepts are memorised better if they are presented as pictures than presented as words, and this is referred to as the picture superiority effect (Nelson, Reed, & Walling, 1976). Based on the picture superiority effect, which suggests an advantage for pictures, we further analysed the effect of the 'cost' of response speed in word and picture stimuli separately. In the fMRI part of the study, we examined brain activities elicited by the current PM paradigm, and focused on the comparison of the neural activations between the 'exemplar' and the 'category' conditions. Previous PM studies using functional neuroimaging techniques has identified a robust lateral vs. medial dissociation in the rostral PFC region (den Ouden, Frith, Frith, & Blakemore, 2005; Gilbert, 2011; Gilbert et al., 2009; Okuda et al., 2007; Okuda, Gilbert, Burgess, Frith, & Simons, 2011; Simons, Schölvinck, Gilbert, Frith, & Burgess, 2006; Hashimoto, Umeda, & Kojima, 2011; Okuda et al., 2007). Activations in the lateral rostral PFC (rPFC) were viewed as maintaining a delayed intention (den Ouden, Frith, Frith, & Blakemore, 2005; Gilbert, 2011; Gilbert et al., 2009; Okuda et al., 2011; Reynolds, West, & Braver, 2009; Simons et al., 2006). The medial rostral PFC activation often seen during PM experiments was first identified by Burgess et al. (2003). He proposed that the observed lower medial rPFC activation reflected a mechanism allowing maintenance of attention upon external stimuli (i.e., ongoing events), whereas lateral rPFC activation is involved enhanced attentional focus on internally generated cognitions. This interpretation was further supported by Gilbert, Frith, & Burgess (2005), who contrasted the neural activation that occurs when subjects perform tasks with stimuli presented on the screen against performing the same tasks only in the subjects' mind (ie. in the absence of stimuli). The medial rPFC region was found to activate in the condition where stimuli were externally displayed (stimulus-oriented; SO) compared with doing the task in the absence of seeing the stimuli on the screen (stimulus-independent; SI). This 'rostral PFC attentional gateway' (see Burgess, Dumontheil, & Gilbert, 2007) evidently associated with performance in PM experiments: Benoit, Gilbert, Frith, & Burgess (2011) used a 2 x 2 factorial design to compare PM (PM vs. non-PM) with attentional gateway (SO vs. SI), and found that the medial rPFC were jointly recruited in ongoing vs. PM, as well as SO vs. SI processing. This finding demonstrated that the observed medial rPFC activity during PM performance was the same as that which was involved in differences in SO vs. SI processing. Interestingly, the PM contrast reported in Benoit et al. (2011) was also found to associate with more dorsal part of the medial rPFC than the attentional gateway contrast along the medial line, and this was interpreted as an engagement of future intention, or prospection (see Burgess, Gonen-Yaacovi, & Volle, 2011 for review). This dorsomedial PFC activity has been found to be involved during other cognitions, including making analogical inferences (Volle, Gilbert, Benoit, & Burgess, 2010), detection of similarity between dissimilar targets (Pothos, 2005), comparison between expectation (Summerfield et al., 2006), envisaging farsighted decisions (Benoit, Gilbert, & Burgess, 2011), and apparently plays a proactive role in generating predictions for the future (Bar, 2009). This literature together suggests that the dorsomedial PFC region supports processing of future intentions that vary in relevance or similarity between expected and presented stimuli. Taking the above PM fMRI literature as a whole, we first examined if the current PM experiment elicited the standard lateral vs. medial dissociation in the rPFC region between the PM and the ongoing tasks established by Burgess et al. (2001; 2003). After confirming that the novel PM paradigm evoked a PM-like neural network, we next compared the neural activities when processing ‘exemplar’ and ‘category’ PM targets. For this comparison, McDaniel, LaMontagne, Beck, Scullin, & Braver (2013) used fMRI and identified a distinct neural network between focal vs. nonfocal PM processing. In the focal PM blocks, the PM cue was a particular word (e.g., table), and in the non-focal PM blocks, the PM cue was a particular syllable (e.g., tor). The result highlighted the distinction between sustained activities (i.e., ‘block’ effect in focal and non-focal PM blocks) in attentional control areas including rPFC region, and transient activities (i.e., ‘trial’ effect between correct PM trials in focal and non-focal blocks) in ventral brain regions. This suggested PM cues differing in focality were involved with two different neural routes, and further supported the multi-process theory by showing PM performance required both top-down attentional control and bottom-up spontaneous retrieval. In the current PM experiment, we further controlled the contribution of the TAP and repetitive priming effects, which affected PM performance more on the perceptual level, and supposedly was related to the bottom-up route described in McDaniel et al., (2013). Therefore, after the TAP and repetitive priming effect to PM cue detection were controlled, we hypothesised that the difference between detecting exemplar and category PM targets was the strength between the encoded item and the expected PM target. In other words, we hypothesised that the process for matching a category to the PM target involved brain regions would be related to make associations between concepts and/or determining what one expects to respond to (i.e., sculpting response space). By contrast, the semantic 'distance' between an encoded exemplar and the forthcoming target is relatively 'negligible', since they were the identical items, albeit in different format in the current PM paradigm. The matching process presumably did not require much associative link. In previous relating fMRI studies, Dolan and Fletcher (1997) revealed that the left dorsolateral PFC region was involved with formation of associations between study materials. This left dorsolateral PFC region was also found to play an important role in cognitive functions relating to 'sculpting response space'. In Fletcher, Shallice, & Dolan (2000), brain activations between the formations of distantly linked word pairs and closely linked word pairs were compared with each other. The result found greater activity for distantly linked word pairs than closely linked pairs in the left dorsolateral PFC region (BA46, MNI: -44, 26, 18). This left dorsolateral PFC region was not only involved with the formation of associative links, but also played an important role in making actions that varied in ‘response space’. Frith, Friston, Liddle, & Frackowiak (1991) used PET to examine the cerebral blood flow associated with willed and routine acts. The results identified that willed, open-ended acts, compared with routine, specified acts, were associated with increased activations in the left dorsolateral PFC region (BA46, MNI: -43, 29, 20). These two studies highlighted that the left dorsolateral PFC activity was linked to semantic associative processing varying in specificity. As a result, we hypothesised that the transient brain activation (e.g., brain activity to correct PM detection trials) for category PM targets would be higher in the left dorsolateral PFC region, compared with exemplar PM targets. Furthermore, without the contribution of bottom-up, spontaneous retrieval processing from the TAP and repetitive priming effects that favoured the ‘exemplar’ PM condition, we hypothesised that analysis for sustained activity (e.g., brain activation throughout the whole block) would show enhanced left dorsolateral PFC activation in the ‘category’ PM blocks, compared with the ‘exemplar’ PM blocks. For exploratory purposes, we also examined the effect of modality (picture vs. word stimuli), and the neural activities during PM encoding and the classification process during the ‘odd one out’ procedure.

8.2 Methods of the prospective memory test

Subjects

Seventeen subjects participated in this PM experiment. All subjects were right-handed, had normal or corrected-to-normal vision with no history of neurological or psychiatric disorders. Before the experiment, all subjects were given written informed consent, and received £20 reimbursement for their participation.

One subject was excluded due to chance performance on the baseline ongoing task. Hence sixteen subjects (10 males, mean age=23.69, ranged from 19-32 years) were included for further analysis.

Experimental design

The basic structure of the PM experiment

The PM experiment used a 2 x 2 factorial design, where the two factors were the 'type' of the PM targets and the 'modality' of the stimuli during the PM task. The 'type' of the PM targets could be either a specified item (the 'exemplar' condition) or an unspecified item that belonged to a category (the 'category' condition). The 'modality' of the stimuli referred to the format of the experimental materials presented during the 'lighter item' ongoing task, which can be either pictures (the 'picture' condition) or words (the 'word' condition). The PM experiment was divided into four sessions, and each session contained 20 blocks. As is the standard setup for neuroimaging PM paradigms, there was a 'baseline' ongoing-only (OG-only blocks) condition that required performing the ongoing task, and experimental conditions where an additional PM task was embedded within the ongoing task (PM blocks) that required maintaining a PM intention (see Tabel 8.1 for the terminology used in the current PM experiment). Each session included 20 blocks, and 4 of the 20 blocks were the 'baseline' OG-only blocks. The other 16 blocks in the same session were the 'PM' blocks, where subjects were required to perform the ongoing task, and simultaneously maintain a PM intention.

Table 8.1. The terminology used and its definition in the current PM experiment.

Terminology	Definition
The odd one out procedure	To odd one out by identifying the odd item or the two similar items.
The OG task (the lighter item task)	To choose the item that weights the least amongst the two items presented side-by-side.
OG-only blocks	OG blocks where no PM intention is being implemented.
OG-uncontaminated [a]	OG-only blocks that are performed *before* any PM instruction is given.
OG-contaminated	OG-only blocks that are administered *after* a PM instruction has previously been implemented.
PM blocks	Blocks where a PM instruction has been given, and subjects are expecting to see a PM target.
PM trials	The specific trials where a PM target is available to subjects.
OG-PM trials	This refers to the OG trials (besides PM trials) during PM blocks.

[a] All the subjects in the current PM study are given PM instructions, which makes all the OG-only blocks 'contaminated'.

The odd one out procedure

As one of the three manipulations of the current PM experiment, we asked subjects to do an 'odd one out' procedure to work out the PM target by themselves as part of the PM encoding stage. In the 'odd one out' procedure, three items were presented horizontally on the screen, and the items were either in verbal or non-verbal (picture) formats. Two of the three items belonged to the same category whilst the third item was from a different category. In the 'OG-only' blocks, the non-verbal items in the 'odd one out' procedure were horizontal or vertical lines shown in white on a black background, whereas the verbal items were either the letters 'H' or 'P'. Subjects were required to detect the repeated or odd stimulus, but no further encoding process was required. In the 'PM' blocks, the items appearing in the 'odd one out' procedure were pictures showing, or words describing, common objects. Subjects were required to detect the odd one out, and further to remember either the category of the two similar items in the 'category' condition, or the identity of the odd item in the 'exemplar' condition.

The ongoing task of the PM experiment: weight judgement

After the 'odd one out' procedure in each block, subjects were required to perform a 'lighter item' task as the ongoing task of our PM experiment. In the 'lighter item' task, two items were presented horizontally on the screen, which would be either pictures showing or words describing common objects. Subjects were required to choose the item that weighed the least (i.e. was the lighter) amongst the two items. One of the three critical manipulations in the current PM experiment was the cross-modality design between the format of PM targets encoded during the 'odd one out' procedure and the format in the 'lighter item' task. The modality of the items presented was always the opposite between the two stages, i.e., if pictures were shown during the 'odd one out' procedure, words would be shown in the subsequent 'lighter item' task, and vice versa. As the 'modality' factor of the PM experiment, for blocks using picture stimuli in the 'lighter item' task were labelled as the 'picture' condition, and blocks using word stimuli in the 'lighter item' task were labelled as the 'word' condition. The PM target embedded in each PM block was different, and subjects were reminded that the encoded PM target in each block applied to that particular block only before administering the experiment.

The 2 x 2 factorial design (type x modality)

In the 'PM' blocks, subjects were required to perform the 'lighter item' task, and simultaneously maintain the encoded PM target during the preceding 'odd one out' procedure in the same block. If the PM target was successfully recognised, they needed to remember to respond to that PM target. As one of the three manipulations of the current PM experiment, each 'PM' block contained only one PM target. In the 16 'PM' blocks of one session, 4 of the PM targets were exemplar targets in word format (the exemplar-word condition), 4 of the PM targets were exemplar targets in picture format (the exemplar-picture condition), 4 of the PM targets were category targets in word format (the category-word condition), and 4 of the PM targets were category targets in picture format (the category-picture condition). The remaining 4 'OG-only' (contaminated) blocks in the same session were served as the 'baseline' blocks for each corresponding 'PM' blocks. All the blocks were presented pseudorandomly within each session, e.g., one of each exemplar-word, exemplar-picture, category-word, category-picture block, along with an 'OG-only' block formed a 'set', and there were four sets in each session, with a constraint of no blocks in the same condition appeared consecutively.

Procedure

In the PM experiment, the duration of each block was 28 seconds. At the beginning of each block, an instruction saying either 'ODD ITEM?' or 'SIMILAR ITEMS' was presented on the screen for 2 seconds. Based on the instruction, subjects were instructed to identify the odd item or the two similar items in the following 'odd one out' procedure. In this 'odd one out' procedure, three items were presented on the screen, and the instruction remained at the bottom of the three items. Subjects were required to respond by pressing one of three assigned keys on a response box when instructed 'ODD ITEM?', and by pressing two of the three keys sequentially when instructed 'SIMILAR ITEMS'. Subjects were allowed to press the same key multiple times to un-select or re-select the item if necessary. The duration allowed for answering the odd one out questions was 5 seconds. After the 5 second limit, in the 'OG-only' blocks, a cue saying 'WAIT' appeared at the bottom of the three items and subjects were required to do nothing for the next 3 seconds. In the 'PM' blocks, a cue saying 'REMEMBER IT' appeared at the bottom instead and subjects were required to remember the odd item as the PM target in the 'exemplar' condition. Alternatively, in the 'category' condition, subjects were required to remember the category that the two similar items belonged to, and this was the PM target (see Figure 8.1). The duration for encoding the PM target was 3 seconds.

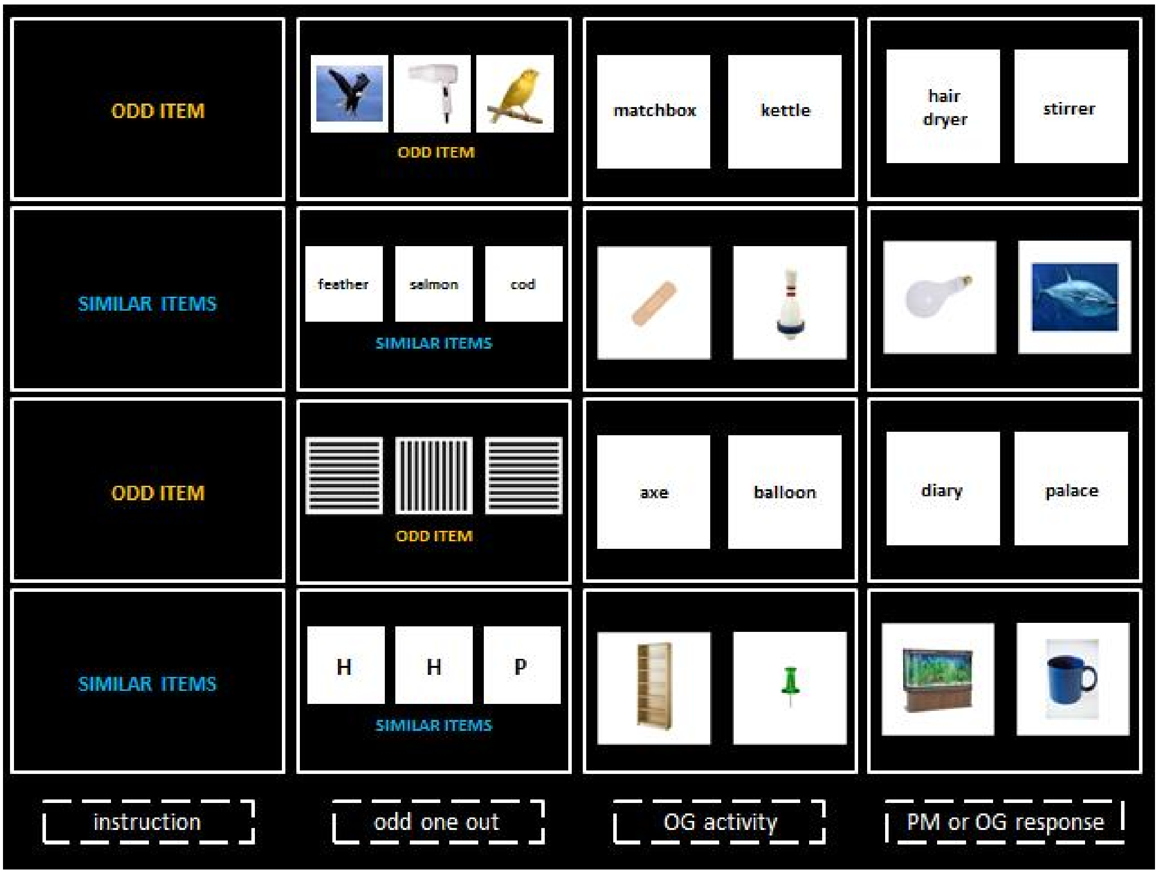


Figure 8.1. The experimental procedure of the PM experiment. The first row demonstrates the exemplar-word condition in 'PM' blocks, the second row demonstrated the category-picture condition in 'PM' blocks, the third row demonstrated the exemplar-word condition in 'OG-only' blocks, and the fourth row demonstrated the category-picture condition in 'OG-only' blocks.

The duration of the subsequent 'lighter item' block was fixed at 16 seconds. Based on the picture superiority effect, compared with word stimuli, response speed should be faster to picture stimuli. This acceleration of response speed would inevitably lead to an exposure of more trials in the picture condition, and subsequently lead to an unequal proportion of PM targets between the 'picture' and the ‘word’ conditions. In order to control for this potential bias accompanied by different stimulus modality, we optimised the duration of each trial based on a pilot study using eight subjects. Hence, during the ‘lighter item’ ongoing task, the two items appeared on the screen for at least 1.5 seconds. If a response was made faster than 1.5 seconds, the response was registered and the two items remained on the screen until 1.5 seconds from the trial onset. If no response was made up to 2.5 seconds from the trial onset, no response would be registered for that trial and the next trial appeared on the screen right away. As a result, the number of trials in the ‘lighter item’ task would be in average 7 -11 trials, which made the proportion of PM targets approximately 9%-15% of total trials, depending on the response pace of the individual (see Table 8.2).

Table 8.2. The experimental design of the PM experiment, which included the number of blocks, number of PM targets, estimated trial number, and the PM proportion in each condition.

Condition	Number of blocks	Number of PM target	Time limit total (sec.)	Time limit per trial (sec.)	Trial numbers in each block	PM proportion in each block (%)
OG-only						
Exemplar-Word	1	0	16	1.5 ~ 2.5	6.4 ~ 10.7	N/A
Exemplar-Picture	1	0	16	1.5 ~ 2.5	6.4 ~ 10.7	N/A
Category-Word	1	0	16	1.5 ~ 2.5	6.4 ~ 10.7	N/A
Category-Picture	1	0	16	1.5 ~ 2.5	6.4 ~ 10.7	N/A
PM						
Exemplar-Word	4	1	16	1.5 ~ 2.5	6.4 ~ 10.7	9.4 ~ 15.6
Exemplar-Picture	4	1	16	1.5 ~ 2.5	6.4 ~ 10.7	9.4 ~ 15.6
Category-Word	4	1	16	1.5 ~ 2.5	6.4 ~ 10.7	9.4 ~ 15.6
Category-Picture	4	1	16	1.5 ~ 2.5	6.4 ~ 10.7	9.4 ~ 15.6

The PM target in each ‘PM’ block would be presented in a pseudorandom way, where the trials containing PM targets would be shown at the sixth to the thirteenth second after the onset of each ‘lighter item’ task. The first 32 sets of experimental materials used in the ‘odd one out’ procedure and the later 32 sets were the same items, except that the items were swapped for the ‘type’ factor in the same modality. For example, the pictorial ‘watermelon-strawberry-briefcase’ combination was instructed ‘ODD ITEM?’ in session one. In session three, the same pictorial combination was instructed ‘SIMILAR ITEMS?’ instead, with the position of the three items re-arranged in different order. A 2 second break was presented at the end of the ‘lighter item’ task in each block, and subjects were allowed to take a short break at the end of each session if needed. A six-minute T1-weighted structural scan was conducted between the second and the third session. The entire MRI scanning time for the PM experiment was approximately 50 minutes.

MRI acquisition

A 1.5 T Siemens TIM Avanto scanner was used to acquire both T1-weighted structural images and T2*-weighted echoplanar images (64 x 64; 3.5 x 3.5 mm pixels; echo time, 40 ms) with blood oxygen level-dependent (BOLD) contrast. Each volume comprised 31 axial slices (3.5 mm thick, oriented approximately to the anterior commissure–posterior commissure plane). Functional scans were acquired in four sessions, each comprising 227 volumes (approximately 9 min). Volumes were acquired continuously with an effective repetition time of 2.5 s per volume. The first two volumes in each session were discarded to allow for T1 equilibration effects. Between the second and the third functional scan, a 6 min T1-weighted structural scan was performed.

Data analysis

Functional magnetic resonance imaging data were analyzed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The volumes were realigned, corrected for different slice acquisition times, normalized into 3.5 mm cubic voxels using the Montreal Neurological Institute reference brain and fourth-degree B-spline interpolation, and smoothed with an isotropic 8 mm full-width half-maximum Gaussian kernel. The volumes acquired during the four sessions were treated as separate time series. For each series, the variance in the BOLD signal was decomposed with a set of regressors in a general linear model (Friston et al., 1995), using a mixed blocked and event-related design (Visscher et al., 2003). The regressors for the 'odd one out' task and the 'lighter item' task were modelled using boxcar design, and the regressors for PM-hit trials were modelled using delta function. Separate regressors coded for (1) odd one out – 'OG-only', (2) odd one out – 'PM', (3) encode – 'OG-only', (4) encode – 'PM', (5) lighter item task – 'OG-only', (6) lighter item task – 'PM', (7) PM-hit trials. These seven regressors were coded separately for the exemplar-word, exemplar-picture, category-word and category-picture blocks, which made 28 regressors. We further set up two additional regressors, one for modelling PM-miss trials and the other one for excluded blocks, i.e., the entire block was excluded when mistakes were made during the 'odd one out' task, which comprised 12 excluded blocks from the total 1280 blocks (20 blocks x 4 sessions x 16 subjects). All the 30 regressors were aligned to the onset of each event modelled by either boxcar or delta function. The events were convolved with a canonical hemodynamic response function, and the duration for the 'odd one out' task was 5 seconds, encoding for 3 seconds, the 'lighter item' task for 16 seconds, and PM-hit trials for 0 second. These regressors of interest, together with the additional regressors representing residual movement-related artefacts and the mean over scans, comprised the full model for each session. The data and model were high-pass filtered using a cut-off of 1/128 Hz.

Parameter estimates for each regressor were calculated from a least mean squares fit of the model to the data. Effects of interest were assessed in a random-effects analysis as follows. The parameter estimates representing all regressors were first contrasted between the 'PM' conditions and the corresponding 'OG-only' conditions, i.e., the contrast images for odd one out – 'PM' versus odd one out – 'OG-only' in the exemplar-word condition. All the resulting contrast images were then entered into different factorial design ANOVA using non-sphericity correction (Friston et al., 2002), including separate GLM models for the 'odd one out', PM encoding, and the 'lighter item' task. The 2 x 2 repeated measures ANOVA entered for analysis represented the factors crossing the 'PM type' factor: exemplar vs. category, and the 'modality' factor: word vs. picture, which resulted in analysis of PM encoding during the 'odd one out' task and PM retrieval during the 'lighter item' task in the EW, EP, CW, and CP conditions. Appropriate contrasts for effects of interest were conducted at the second level, applying a height threshold of $p<0.001$ uncorrected in conjunction with an extent threshold determined by SPM8 to achieve $p<0.05$ family-wise error correction for multiple comparisons across the whole brain volume.

8.3 Behavioural and fMRI part of the result

<u>Behavioural part of the result</u>

The behavioural part of the analysis focused on the performance during the 'lighter item' task, and was divided into two parts. In the first part, in order to examine the difference between PM-related (e.g., the 'PM' blocks) and PM-unrelated (e.g., the 'OG-only' blocks) effect, we first collapsed the 'type' and the 'modality' factors by comparing the overall effect between the 'OG-only' and the 'PM' blocks. In the second part, we examined the 'OG-only' and the 'PM' blocks separately. Given that no PM-related actions were required in the 'OG-only' blocks, we collapsed the type factor and only examined the 'modality' effect between the word and the picture conditions. In the 'PM' blocks, we examined the effect of 'type' and 'modality', as well as the 'type' x 'modality' interaction. Furthermore, we also examined the 'type' and the 'modality' effect to performance to the PM target trials in the 'PM' blocks.

The accuracy for the ongoing (weight judgement) task

The accuracy for the 'lighter item' task in each condition were summarised in Table 8.3. In the first part of the analysis, the 'type' and the 'modality' factor were collapsed together, and a paired t test showed a significant difference between the 'OG-only' and the 'PM' blocks ($t(15)=-2.552$, $p=0.022$), showing subjects had significantly higher accuracy in the 'OG-only' blocks than in the 'PM' blocks. In the second part, analysis of the accuracy in the 'OG-only' blocks collapsing the 'type' factor identified a significant effect of 'modality' ($t(15)=2.806$, $p=0.013$), where the accuracy was significantly higher in the 'picture' condition than in the 'word' condition. For the analysis in the 'PM' blocks, repeated measures ANOVA found a significant main effect of 'modality' ($F(1,15)=37.126$, $p<0.001$), showing significant the accuracy was significantly in the 'picture' condition than in the 'word' condition. No significant main effect on 'type' and type x modality interaction were found.

Table 8.3. The accuracy for the 'OG-only' and the 'PM' blocks in the 'lighter item' task, and the main effect of different factors were presented in separate columns.

			mean	SD	Main effect of		
					block	type	modality
OG-only							
	Overall		0.91	0.01	p=0.022		
		Word condition	0.89	0.05			p=0.013
		Picture condition	0.92	0.04			
OG-PM							
	Overall		0.89	0.01			
		Exemplar-Word condition	0.85	0.08		p=0.669	p<0.001
		Exemplar-Picture condition	0.93	0.03			
		Category-Word condition	0.85	0.06			
		Category-Picture condition	0.93	0.03			

The reaction time for the 'lighter item' task

The reaction times for the 'lighter item' task in each condition are summarised in Table 8.4. In the first part of the analysis, the 'type' and the 'modality' factor were collapsed together, and paired t-test did not find a significant effect between the 'OG-only' and the 'PM' blocks ($t(15)=-1.457$, $p=0.166$). In the second part, analysis of the 'OG-only' blocks using a paired t test identified a significant effect of 'modality' ($t(15)=11.288$, $p<0.001$), where subjects responded significantly faster in the 'picture' condition than in the 'word' condition. For the analysis of the 'PM' blocks, repeated measures ANOVA revealed a significant effect of 'modality' ($F(1,15)=334.663$, $p<0.001$), which revealed that the response speed was significantly faster in the 'picture' condition than in the 'word' condition. No significant 'type' or type x modality interaction was found.

Table 8.4. The reaction time (msec.) for the 'OG-only' and the 'PM' blocks in the 'lighter item' task, and the main effect of different factors are presented in separate columns.

			mean	SD	Main effect of		
					block	type	modality
OG-only							
	Overall		1079.1	50.2	p=0.166		
		Word condition	1222.7	218.2			p<0.001
		Picture condition	935.4	196.0			
OG-PM							
	Overall		1093.3	46.8			
		Exemplar-Word condition	1247.6	201.8		p=0.415	p<0.001
		Exemplar-Picture condition	933.0	176.7			
		Category-Word condition	1251.4	201.0			
		Category-Picture condition	941.2	184.0			

In Einstein et al. (2005), it was shown that the 'cost' of the response speed between the ongoing and the PM task was significant in the non-focal condition, but not significant in the focal PM condition. Therefore, we used the reaction time in the 'OG-only' blocks as the 'baseline', and compared the reaction time in the 'exemplar' and the 'category' conditions of the 'PM' blocks separately by collapsing the 'modality' factor. Paired t tests showed that the difference was not significant when comparing the 'OG-only' blocks from the 'exemplar' condition in the 'PM' blocks ($t(15)=0.999$, $p=0.333$), nor in the 'category' condition ($t(15)=1.82$, $p=0.089$). However, we have identified a strong picture superiority effect showing that picture stimuli were associated with better accuracy and faster response speed than word stimuli. This intrigued us to further analyse the 'cost' of response speed, compared with the baseline 'OG-only' blocks, in the exemplar and the category conditions using word and picture stimuli separately. Analysis of blocks using word stimuli showed that the 'cost' of response speed was significant comparing with the 'OG-only' blocks in the 'category' condition of the 'PM' blocks ($t(15)=-2.3$, $p=0.036$), but the 'cost' was not significant in the 'exemplar' condition of the 'PM' blocks ($t(15)=-2.06$, $p=0.058$). On the other hand, analysis of blocks using picture stimuli revealed that the 'cost' of response speed was not significant either in the 'OG-only' blocks in the 'exemplar' $t(15)=0.017$, $p=0.871$) condition, or the 'category' condition ($t(15)=-0.39$, $p=0.705$) of the 'PM' blocks.

The performance for the PM target trials

The accuracy and the reaction time for the PM target trials in the 'lighter item' task are summarised in Table 8.5. Repeated measures ANOVA of the accuracy to the PM targets in the 'PM' blocks found a significant effect of 'modality'

($F(1,15)=18.798$, $p=0.001$), which showed that the correct detection rate for PM targets was significantly higher for pictures than for words. No significant effect of 'type' or type x modality interaction was found. Repeated measures ANOVA of the reaction time to the PM target trials revealed a significant effect of 'modality' ($F(1,15)=370.246$, $p<0.001$), where the response speed was significantly faster to pictures than to words. No significant effect of 'type' and type x modality interaction was found.

Table 8.5. The accuracy and the reaction time (msec.) for the PM target trials in the 'PM' blocks, and the main effect of different factors are presented in separate columns.

	Accuracy		Main effect of	
	mean	SD	type	modality
Accuracy				
Exemplar-Word condition	0.66	0.19		p=0.001
Exemplar-Picture condition	0.79	0.14		
Category-Word condition	0.64	0.20		
Category-Picture condition	0.79	0.12		
Reaction time				
Exemplar-Word condition	1134.7	199.5		p<0.001
Exemplar-Picture condition	852.4	175.3		
Category-Word condition	1109.1	198.1		
Category-Picture condition	888.1	203.1		

Supplementary analysis

As mentioned in the methodology section, the purpose of setting a 1.5 second minimum duration for each trial was to control for the overall proportion of PM targets in the 'picture' and the 'word' conditions. To examine if this had an effect on the proportion, we examined the trial numbers in the 'lighter item' task (see Table 8.4). We followed the same procedure as for the analysis of the accuracy and the reaction time to investigate the trial numbers in each. In the first stage, paired t tests found no significant difference between the ongoing trials during the 'OG-only' and the 'PM' blocks ($t(15)=0.524$, $p=0.608$). In the second stage, analysis of the 'OG-only' blocks using paired t test found a significant effect of 'modality' ($t(15)=-3.90$, $p=0.001$), which indicated that subjects responded to significantly more trials in the 'picture' condition than in the 'word' condition. In the 'PM' blocks, repeated measures ANOVA also showed a significant main effect of 'modality' ($F(1,15)=32.654$, $p<0.001$), where more trials were processed in the 'picture' condition than in the 'word' condition. But no significant effect of 'type' or type x modality interaction was found.

<u>The fMRI part of the result</u>

Analysis of the brain activation was conducted by two approaches, one measured the activated during the whole block (the sustained effect), and the other investigated the neural activity associated with particular trials (the transient effect).

The sustained brain activation of the lateral vs. medial rostral PFC dissociation

In this section, we included all the trials in the 'PM' and the 'OG-only' blocks to examine the sustained effect by collapsing the 'type' and 'modality' factors during the 'lighter item' task (see Table 8.6 for results). The brain activity in the 'PM' blocks was compared to the 'OG-only' blocks, and the result showed increased activation in the left BA46 region (peak MNI: -40, 28, 24, p(FWE)=0.005). In order to examine if the current PM experiment evoked the 'standard' lateral rPFC activation identified in the previous PM studies (Burgess et al., 2001; 2003; Simon et al., 2006; Okuda et al., 2007; Gilbert et al., 2009), a lenient $p<0.005$ threshold was applied for exploring increased activations in the rPFC region. The lenient threshold located a right lateral PFC activation in BA10 region (peak MNI: 31, 49, 17), and this activation survived from small volume correction using the MNI coordinate of the 'intention retrieval PM' > 'uncontaminated OG' contrast reported in Simons et al. (2006). The analysis of the 'OG-only' blocks compared against the 'PM' blocks in the 'lighter item' task identified a widespread frontal, parietal, and subcortical regions including hippocampus and claustrum (all p(FWE)<0.05). The observed medial rPFC activation was in the medial BA10 region (peak MNI: 10, 60, 24) extending posteriorly to BA8 area (all p(FWE)<0.05) (see Figure 8.2, for illustration).

Table 8.6. Regions showing significant differences in 'sustained' BOLD signals in the 'lighter item' task during the PM and the OG-only blocks.

	Brain region	BA	MNI coordinates *x*	*y*	*z*	p(FWE) [a]	Z_{max}	k
PM blocks > OG-only blocks								
	Middle Frontal Gyrus	BA46	-40	28	24	0.005	4.30	102
	Precentral Gyrus	BA6	-36	0	31			
	Precentral Gyrus	BA6	-50	4	34			
	Middle Frontal Gyrus	BA10	31	49	17	0.049 [b]	2.84	7
PM blocks < OG-only blocks								
	Inferior Parietal Lobule	Claustrum	-36	-11	-5	0.05	5.00	56
	Inferior Parietal Lobule	BA39	-50	-67	41	<0.001	4.78	228
	Inferior Parietal Lobule	BA40	-57	-53	41			
	Parahippocampal Gyrus	BA40	-61	-39	38			
	Parahippocampal Gyrus	Hippocampus	27	-18	-19	0.007	4.75	96
	Parahippocampal Gyrus	BA19	27	-53	-1			
	Paracentral Lobule	BA37	31	-39	-8			
	Precental Gyrus	BA3	17	-35	55	<0.001	4.52	543
	Precental Gyrus	BA4	31	-25	55			
	Angular Gyrus	BA4	38	-18	48			
	Angular Gyrus	BA39	52	-63	34	<0.001	4.42	243
	Middle Temporal Gyrus	BA39	45	-70	31			
		BA21	69	-48	-1			
	Inferior Parietal Lobule	Claustrum	38	-18	-1	<0.001	4.29	207
		BA40	62	-32	41			
	Inferior Fronal Gyrus	Claustrum	34	-14	13			
	Inferior Fronal Gyrus	BA10	52	39	-1	0.047	4.05	57

Superior Frontal Gyrus	BA47	48	42	-8			
Superior Frontal Gyrus	BA8	-15	49	38	0.031	4.01	65
Superior Frontal Gyrus	BA10	10	60	24			
	BA8	-12	42	48			

* Coordinates refer to the Montreal Neurological Institute reference brain. BA refers to approximate (±5mm) Brodmann area

[a] Corrected for multiple comparison across all brain voxels

[b] Small volumue correction using the MNI coordinate in Simons et al. (2006)

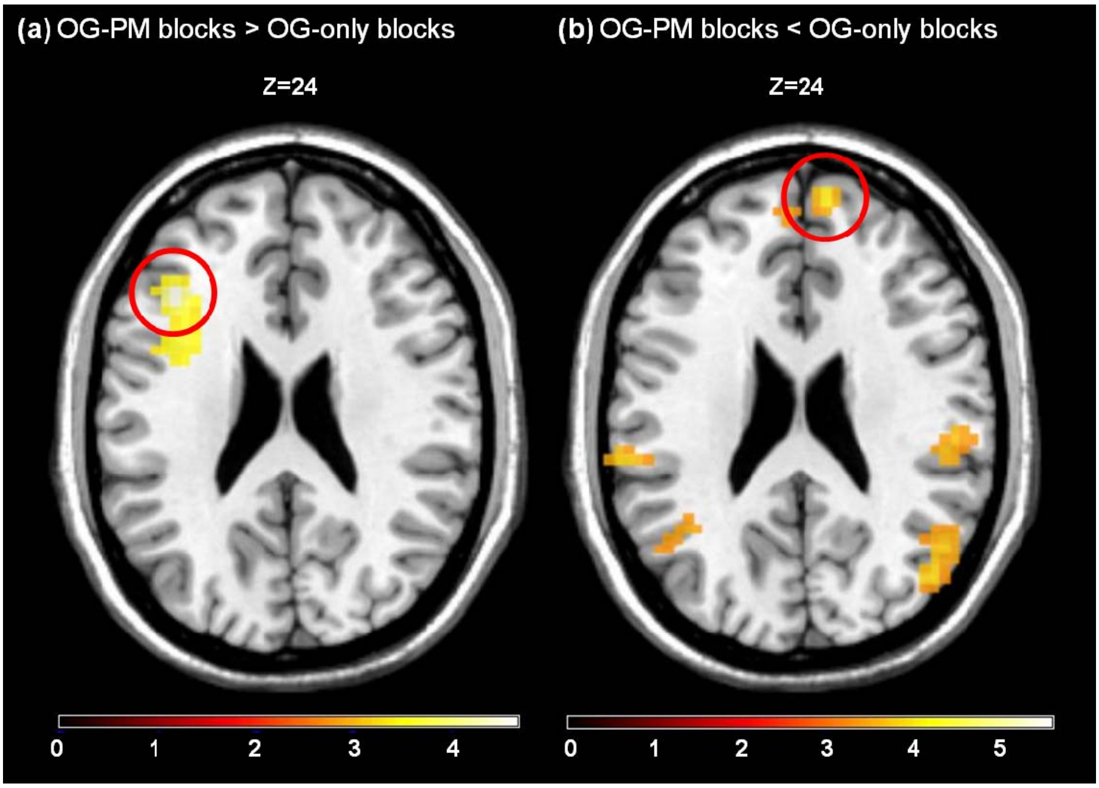


Figure 8.2. Functional imaging results in the 'lighter item' task during the PM and the OG-only blocks. (a) Stronger sustained activation in the left BA46 region when contrasting ‘PM’ blocks to ‘OG-only’ blocks. (b) Stronger sustained activation in the medial BA10 region in the ‘OG-only’ blocks vs. ‘PM’ blocks contrast.

The sustained and transient brain activity between the effect of ‘type’

First, to examine the sustained brain activity between maintaining PM intentions varying in specificity, we compared the sustained brain activation between the ‘exemplar’ and the ‘category’ conditions during the ongoing task (see Table 8.7). Brain activity in the ‘category’ condition compared against the ‘exemplar’ condition revealed strong activations in the occipital and temporal region including fusiform gyrus and middle occipital gyrus (all p(FWE)<0.001). No enhanced activation was found in the ‘exemplar’ vs. ‘category’ contrast. Next, we examined the transient brain activity associated with successful detection of PM targets of varying specificity, and the results are reported in Table 8.7. A paired t test comparing the ‘category’ condition against the ‘exemplar’ condition revealed increased activations in the right inferior parietal lobule and frontal region in left BA46 (MNI: -47, 35, 20, p(FWE)=0.04, see Figure 8.3). No activations were found in the reverse exemplar vs. category comparison.

Table 8.7. Regions showing significant differences in 'sustained' BOLD signals to ‘sustained’ and 'transient' effects during the 'lighter item' task between PM type.

			MNI coordinates				
Brain region	BA	*x*	*y*	*z*	p(FWE) [a]	Z_{max}	k
Sustained block effect							
PM type: Exemplar condition > Category condition							
PM type: Exemplar condition < Category condition							
Fusiform Gyrus	BA37	27	-42	-15	<0.001	4.99	203
Superior Occipital Gyrus	BA19	38	-77	27	<0.001	4.86	317
Middle Occipital Gyrus	BA19	31	-91	6			
Middle Occipital Gyrus	BA18	-33	-88	3	<0.001	4.72	213
Middle Occipital Gyrus	BA18	-26	-95	6			
Middle Occipital Gyrus	BA19	-43	-81	-1			
Interaction: PM type x Modality							
Fusiform Gyrus	BA19	24	-77	-15	0.015	4.43	80
Ligual Gyrus	BA17	17	-91	-1			
Fusiform Gyrus	BA18	20	-84	-12			
Transient trial effect							
PM type: Exemplar condition > Category condition							
PM type: Exemplar condition < Category condition							
Middle Frontal Gyrus	BA46	-47	35	20	0.04	4.34	42
Middle Frontal Gyrus	BA45	-47	35	6			
Inferior Parietal Lobule	BA40	34	-56	45	0.025	3.96	48

* Coordinates refer to the Montreal Neurological Institute reference brain. BA refers to approximate (±5mm) Brodmann area

[a] Corrected for multiple comparison across all brain voxels

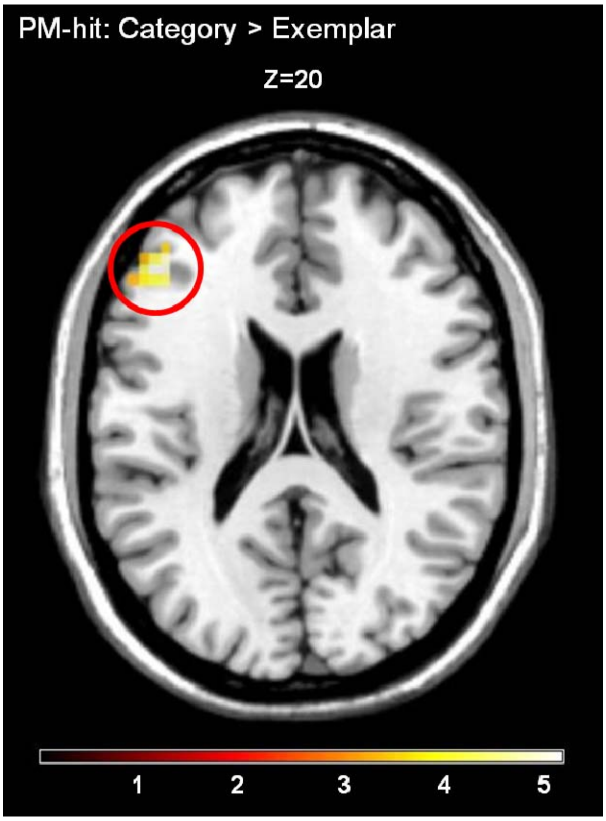


Figure 8.4. The t stronger transient activation for PM hit trials when comparing the 'category' condition to the 'exemplar' condition in the left BA46 region.

Supplementary analysis – the sustained activation between the effects of 'modality'

In the current PM experiment, we used a cross-modality design to control for the TAP and repetitive priming effects to PM performance, which allowed us to examine the effect of 'modality' when using different format of materials in a PM paradigm (see Table.8.8 for results). The analysis of the sustained brain activity in the 'lighter item' task found that the 'word' condition compared against the 'picture' condition elicited strong activity located in the occipital region and frontal region in left BA8/9

(MNI: -22, 42, 45, p(FWE)=0.04). No activations were found in the reverse picture vs. word contrast. Importantly, repeated measures ANOVA identified a significant type x modality interaction in the right fusiform gyrus (MNI: 24, -77, -15, p(FWE)=0.015). Follow-up analysis demonstrated that brain activity was higher in the ‘category’ than in the ‘exemplar’ condition only using picture stimuli ($t(15)=-7.1$, $p<0.001$), but the difference was comparable using word stimuli ($t(15)=-0.05$, $p=0.961$) (see Figure 8.4). The analysis of transient activity associated with successful PM target detection revealed that the ‘word’ condition evoked stronger activations in bilateral occipital region than in the ‘picture’ condition, and the reverse contrast showed stronger activations in the thalamus (see Table 8.8).

Table 8.8. Regions showing significant difference in ‘sustained’ block effects and 'transient' PM-hit trial effects during the 'lighter item' task between modality.

		MNI coordinates					
Brain region	BA	*x*	*y*	*z*	p(FWE) [a]	Z_{max}	k
Sustained block effect							
Modality: Word condition > Picture condition							
Cuneus	BA19	31	-84	27	0.001	4.81	159
Middle Temporal Gyrus	BA19	41	-77	20			
Superior Frontal Gyrus	BA8	-22	42	45	0.04	4.47	60
Superior Frontal Gyrus	BA9	-29	49	34			
Cuneus	BA17	-15	-95	6	<0.001	4.42	254
Cuneus	BA19	-22	-88	27			
Middle Temporal Gyrus	BA19	-36	-81	20			
Modality: Word condition < Picture condition							
Transient trial effect							
Modality: Word condition > Picture condition							
Middle Occipital Gyrus	BA19	38	-81	10	p<0.001	6.81	1632
Fusiform Gyrus	BA19	-26	-53	-15			
Fusiform Gyrus	BA19	34	-70	-15			
Modality: Word condition < Picture condition							
Pulvinar	Thalamus	-8	-25	6	0.042	3.97	45
Pulvinar	Thalamus	10	-35	13			
Ventral Lateral Nucleus	Thalamus	-19	-14	13			

* Coordinates refer to the Montreal Neurological Institute reference brain. BA refers to approximate (±5mm) Brodmann area

[a] Corrected for multiple comparison across all brain voxels

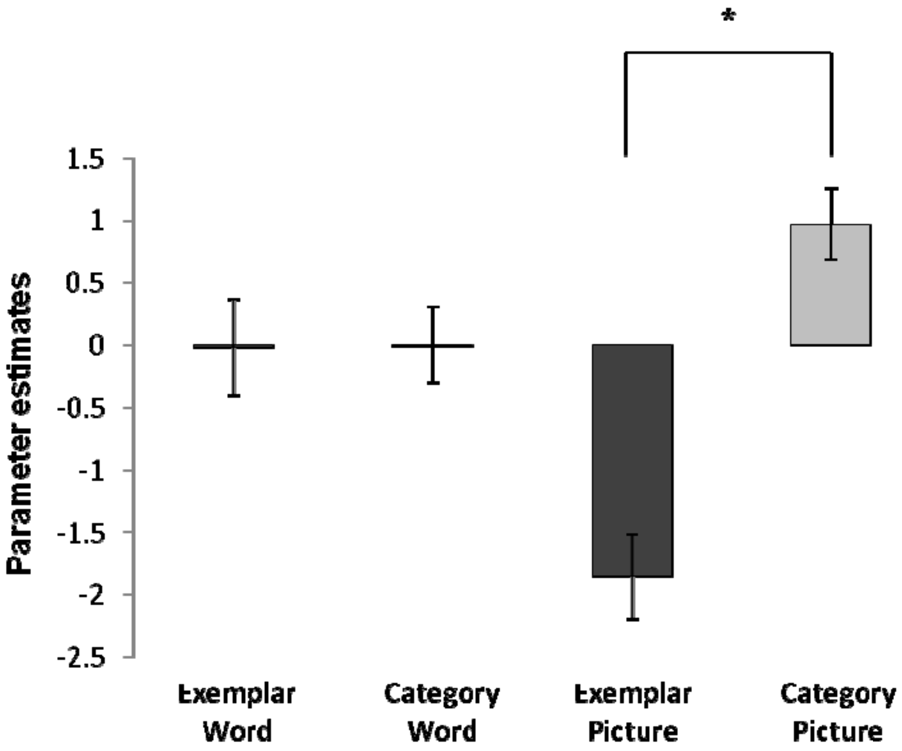


Figure 8.4. The type x modality interaction where stronger sustained activation was found when comparing the 'Category-Picture' condition to the 'Exemplar-Picture' condition, but comparable when comparing the 'Category-Word' condition to the 'Examplar-Word' condition in the right fusiform gyrus..

Supplementary analysis – the sustained activation of the encoding stage

We also examined the sustained brain activity associated with PM encoding during the 'odd one out' procedure following the same procedure as in the 'lighter item' task, and the results were summarised in Table 8.9. When comparing the 'PM' blocks against the 'OG-only' blocks collapsing across the 'type' and the 'modality' factors, increased activations were found in lingual gyrus, bilateral fusiform gyrus (BA19) and dorsal cingulate gyrus in BA24. No activations were found when comparing the ‘OG-only’ blocks with the ‘PM’ blocks. We further investigated the brain activity during the PM encoding stage between the ‘exemplar’ and the ‘category’ conditions. When comparing the ‘category’ condition against the ‘exemplar’ condition, the result demonstrated a strong activations in the PFC region located in medial BA9 (peak MNI: -1, 60, 31, p(FWE)=0.019, see Figure 8.5.) extending posteriorly to BA6. No activations were found in the opposite exemplar vs. category contrast. Comparison between modality (word vs. picture) found no enhanced activations in the word vs. picture contrast or the picture vs. word contrast.

Table 8.9. Regions showing significant differences in 'sustained' effects during PM encoding between experimental conditions.

	BA	MNI coordinates x	y	z	p(FWE) [a]	Z_{max}	k
PM blocks > OG-only blocks							
Fusiform Gyrus	BA19	-36	-74	-19	<0.001	5.46	1144
Cuneus/Ligual Gyrus	BA17/18	-15	-95	-1			
Fusiform Gyrus	BA19	31	-81	-19			
Cingulate Gyrus		-22	4	31	0.011	4.89	76
Cingulate Gyrus	BA24/32	-15	7	34			
		-15	11	20			
PM blocks < OG-only blocks							
PM type: Exemplar condition > Category condition							
PM type: Exemplar condition < Category condition							
Superior Frontal Gyrus	BA9	-1	60	31	0.019	4.33	66
Superior Frontal Gyrus	BA9	-12	49	31			
Superior Frontal Gyrus	BA8	24	42	41	0.009	4.04	80
Superior Frontal Gyrus	BA6	10	21	52			
Medial Frontal Gyrus	BA8	17	32	38			
Modality: Word condition > Picture condition							
Modality: Word condition < Picture condition							

* Coordinates refer to the Montreal Neurological Institute reference brain. BA refers to approximate (±5mm) Brodmann area

[a] Corrected for multiple comparison across all brain voxels

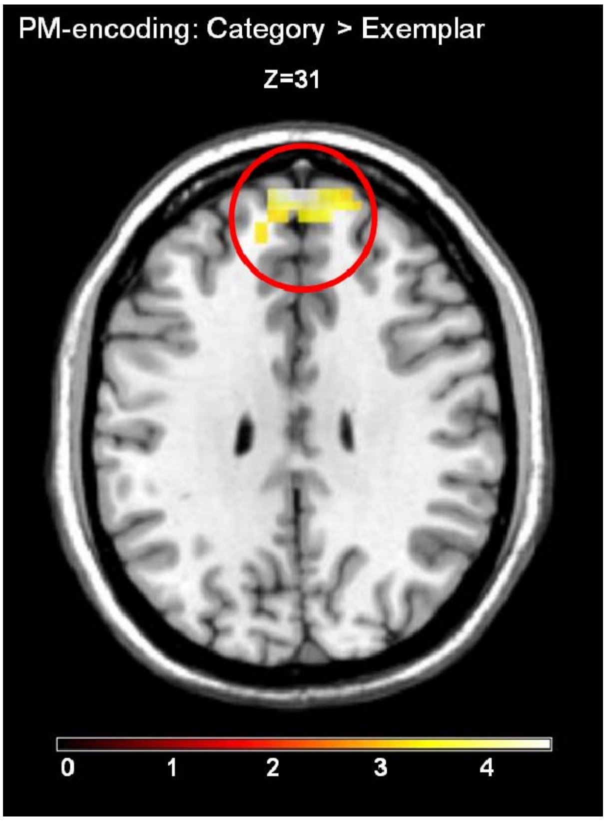


Figure 8.5. The activation that showed stronger sustained activation during PM encoding when contrasting the 'category' condition to the 'exemplar' condition in the dorsomedial PFC region.

Supplementary analysis – the sustained activation of the odd one out stage

We also analysed the sustained brain activity associated with classification process during the 'odd one out' procedure, and the results were summarised in Table 8.10. When comparing the 'PM' blocks against the 'OG-only' blocks collapsing across the 'type' and the 'modality' factors, widespread activations were found in frontal region including bilateral BA46/9, as well as in occipital region (bilateral BA18). The reversed 'OG-only' blocks vs. the 'PM' blocks contrast showed stronger activities in parietal region and frontal region in the medial rPFC region (peak MNI:

10, 60, 24, p(FWE)<0.001) extending posteriorly from BA10 to BA8. For the comparison between the 'type' of PM targets, no increased activity was found in the exemplar vs. category contrast, or the reversed category vs. exemplar contrast. On the other hand, analysis of the 'modality' factor revealed that, in the word vs. picture contrast, a stronger activation was found in the occipital region (BA18) extended anteriorly to fusiform gyrus (BA37). The reversed picture vs. word contrast revealed stronger activities in occipital region (BA18) and bilateral sensory cortices including BA3 and BA6.

Table 8.10. Regions showing significant differences in 'sustained' effects of the classification process during the 'odd one out' procedure between experimental conditions.

	BA	MNI coordinates x	y	z	p(FWE) [a]	Z_{max}	k
PM blocks > OG-only blocks							
Inferior Occipital Gyrus	BA18	38	-88	-8	p<0.001	Inf	844
Fusiform Gyrus	BA37	34	-60	-15			
Superior Occipital Gyrus	BA19	31	-74	27			
Inferior Occipital Gyrus	BA18	-33	-91	-8	p<0.001	Inf	1079
Inferior Occipital Gyrus	BA18	-40	-84	-8			
Fusiform Gyrus	BA37	-40	-49	-19			
Precentral Gyrus	BA6	-36	4	31	p<0.001	7.31	899
Middle Frontal Gyrus	BA46	-43	28	24			
Middle Frontal Gyrus	BA46	-43	32	13			
Superior Frontal Gyrus	BA8	-5	18	48	p<0.001	6.62	228
Middle Frontal Gyrus	BA46	41	28	20	p<0.001	5.45	327
Precentral Gyrus	BA9	38	11	31			
Middle Frontal Gyrus	BA6	31	0	48			
PM blocks < OG-only blocks							
Supramarginal Gyrus	BA40	55	-56	31	p<0.001	4.84	204
Supramarginal Gyrus	BA40	55	-39	31			
Inferior Parietal Lobule	BA40	62	-28	27			
Superior Frontal Gyrus	BA10	10	60	24	p<0.001	4.48	170
Superior Frontal Gyrus	BA8	20	49	41			
Medial Frontal Gyrus	BA9	20	56	27			
Cuneus	BA18	13	-91	20	p=0.053	4.24	48
PM type: Exemplar condition > Category condition							

PM type: Exemplar condition < Category condition							
Modality: Word condition > Picture condition							
Fusiform Gyrus	BA37	34	-60	-15	p<0.001	6.45	635
Inferior Occipital Gyrus	BA18	41	-84	-5			
Fusiform Gyrus	BA37	27	-42	-15			
Middle Occipital Gyrus	BA18	-40	-84	3	p<0.001	6.37	549
Fusiform Gyrus	BA37	-29	-49	-15			
Fusiform Gyrus	BA19	-29	-63	-15			
Modality: Word condition < Picture condition							
Ligual Gyrus	BA19	24	-63	3	p<0.001	4.6	270
Ligual Gyrus	BA18	-15	-74	6			
Middle Occipital Gyrus	BA18	-12	-98	17			
Middle Frontal Gyrus	BA6	31	4	41	p=0.026	4.22	60
Middle Frontal Gyrus	BA6	34	0	55			
Middle Frontal Gyrus	BA6	27	-7	55			
Postcentral Gyrus	BA3	-40	-18	52	p<0.001	3.93	154
Precentral Gyrus	BA6	-36	-11	45			
Inferior Parietal Lobule	BA40	-33	-39	41			

* Coordinates refer to the Montreal Neurological Institute reference brain. BA refers to approximate (±5mm) Brodmann area

[a] Corrected for multiple comparison across all brain voxels

8.4 Discussion of the prospective memory test

Behavioural effect on OG-only vs. PM trials

The PM experiment used a cross-modality design and a novel setting for PM encoding to control for the potential TAP and repetitive priming effects on PM performance. In the behavioural part of the study, when comparing the accuracy for the 'lighter item' task between the baseline 'OG-only' and experimental 'PM' blocks by collapsing the 'type' and the 'modality' factors, the result revealed that subjects responded more accurately in the 'OG-only' blocks than in the 'PM' blocks. This suggested that maintenance of future intentions in the 'PM' blocks interfered with the ongoing activity, and resulted in lower accuracy on identifying the item that weighted lighter amongst the two items. On the other hand, analysis of reaction time found that, despite the averaged response speed was faster in the 'OG-only' blocks than in the 'PM' blocks, the difference was not significant. This insignificant 'cost' between the PM-unrelated and the PM-related conditions was inconsistent with the finding demonstrated in previous PM studies (e.g., Burgess et al., 2003; Einstein et al., 2005), where significantly slower reaction times were identified when subjects performed an additional PM task compared with the baseline ongoing situation. Nevertheless, the current PM experiment used a cross-modality design and found robust picture superiority effect. To examine if there is any modality-specific difference, we further analysed the blocks using words and pictures in the 'lighter item' task separately. The result showed that reaction time was significantly slower in the 'PM' blocks than the 'OG-only' blocks when using word stimuli (PM blocks: 1249.51 msec., OG-only: 1222.72 msec.; $t(15)=-2.334$, $p=0.034$), which was consistent with the finding observed in Einstein et al. (2005). However, in blocks using picture stimuli, the 'cost' between the 'PM' blocks and the 'OG-only' blocks remained insignificant (PM blocks: 937.11 msec., OG-only blocks: 935.40 msec.; $t(15)=-0.122$, $p=0.905$). This suggests a possible format-specific distinction, where the 'cost' between PM-related and PM-unrelated conditions was more prominent using verbal stimuli than using non-verbal stimuli. Furthermore, this distinction between modality supported the picture superiority effect, i.e. acceleration when responding to pictorial stimuli and/or attenuation to the interference contributed by maintaining delayed intentions.

<u>Behavioural effects of exemplar vs. category PM intentions</u>

Next, we examined the effect of 'type' by comparing performance between the 'exemplar' and the 'category' conditions in the 'PM' blocks of the 'lighter item' task. The result found no significant 'type' effect on accuracy and reaction time. We did not find a significant effect of 'type' that demonstrated in Einstein et al. (2005),where subjects responded significantly slower when maintaining non-focal intentions, compared with focal intentions. A possible explanation was the single PM target block design in the current PM experiment, where each block contained only one PM target, and subjects were required to work out a new PM target that applied to that particular block only at the beginning of each block. As a result, the exemplar PM target in the current PM experiment was different between each block, but the focal PM target in Einstein et al. (2005) remained the same throughout the task. It is possible that this critical difference made subjects develop a strategy to cope with processing one-time PM targets (e.g., current PM experiment) vs. multiple, repeated PM targets (e.g., Einstein et al., 2005). For example, in Einstein et al. (2005), subjects might adapt a strategy specifically for maintaining the repetitive focal PM intention, and the repetitive exposure of the identical PM targets might free up the attentional load in the focal PM condition as the test progressed. On the other hand, the non-focal PM target shared only partial features between each other, and subjects needed to engage in relatively higher effort to maintain non-focal PM intentions. As a result, it is possible that the response speed accelerated as the PM test progressed in the focal PM condition, and led to significantly faster 'averaged' reaction times in the focal PM condition, compared with the non-focal PM condition, when taking the PM performance as a whole. By contrast, in the current PM experiment, each PM intention was different from each other in each block, regardless of the exemplar or the category conditions. This constant change of the PM targets might limit the observed advantage of focal processing identified in Einstein et al. (2005), which were possibly contributed by, to a certain degree, the level of shared features between PM intentions.

For the analysis of the PM trials where subjects correctly identified the PM targets revealed no significant effect of 'type' on accuracy and reaction time between the 'exemplar' and the 'category' conditions. This was inconsistent with the result in Einstein et al. (2005), where PM accuracy was significantly higher for detecting focal targets than for non-focal targets. A possible explanation was the cross-modality design in the current PM experiment, which was originally introduced to control for the effect of repetitive priming to PM detection. To elaborate on this manipulation to PM target detection, for example, in Einstein et al. (2005), the word 'dormitory', as the focal PM target, was pre-exposed to subjects before administering the PM task, but the syllable 'tor', as the non-focal PM target, appeared only a fraction to subjects in advance. As we speculated earlier, non-focal PM targets had a relatively lower level of repetitive features compared with focal PM targets. The advantage of focal processing might be partially contributed to by the repetitive priming effect, where a stimulus that was previously experienced would lead to quicker and better performance on the later exposure of the same stimulus. In the current PM experiment, the cross-modality design eliminated the potential benefits coming from repetitive priming on the perceptual level, and, if any, subjects could only rely on a priming effect on the conceptual level. As a result, the null result of PM target detection between the 'type' factor suggested that exemplar PM targets, or targets having higher specificity, were not sufficient enough to produce an advantage of target detection, compared with category PM targets, or targets having lower specificity. Moreover, the single PM target block design might also contribute to this null result between the exemplar and category conditions. It is possible that the difficulty in identifying the very first PM target, regardless of exemplar/category or focal/non-focal conditions, would be identical or comparable. For example, given that focal PM targets would re-appear in identical feature every time (e.g., always 'dormitory'), whereas non-focal PM targets differed in fragments every time (e.g., his'tor'y, 'tor'nado, 'tor'toise), the advantage for processing focal PM target might become more prominent as the test progresses. In the current PM experiment, the single PM target block design highlighted a possible equivalence of identifying PM targets that varied in specificity, especially under the circumstances that the TAP and repetitive priming effects were controlled. Besides the experimental manipulation, it was proposed that subjective factors like a higher level of emphasis on the PM instruction could result in greater monitoring for the PM target, and subsequently lead to better PM target detection (Einstein et al., 2005). Therefore, it is also possible that the single PM target block design in the current PM experiment made subjects prioritise the processes relating to PM targets, given that the PM target changed every block, which might diminish the advantage of spontaneous focal processing which required a mapping mechanism (c.f., Moscovitch, 1994). Lastly, the aim of the current PM study was to examine the effect of PM targets varying in specificity, which was one of the many factors that distinguished focality between PM targets. The inconsistent findings reported here did not fundamentally conflict with the core idea of the multi-process theory, which highlights a multi-pathway that subjects can rely on for spontaneous or monitoring processes under different circumstances in PM activities. The behavioural result perhaps suggested that the exemplar vs. category distinction we manipulated was not sufficient to elicit a mechanism that weighted between spontaneous retrieval and attentional monitoring processes to PM performance.

Behavioural effect on word vs. picture stimuli

The other factor we manipulated in the current PM experiment was the modality of the experimental materials. In this cross-modality design, items presented in word format during the 'odd one out' procedure was presented in picture format in the subsequent 'lighter item' task, and vice versa. Previous psychological studies comparing performance on items presented in verbal vs. non-verbal formats have revealed a robust picture superiority effect (Nelson, Reed, & Walling, 1976), where concepts are memorised better when presented as pictures than presented as words. In the current PM experiment, analysis of the main effect of modality in the 'lighter item' task found that accuracy was higher and response speed was faster to pictures than to words, and this superiority effect for processing pictures was also evident for PM target trials. Several theories have been proposed to explain this format-specific advantage for pictures. For example, the dual coding theory (Paivio, 1986; 1991) proposed that the advantage occurs during the encoding stage, where pictures are dually encoded by generating both verbal and image codes, whereas word stimuli are generated only using verbal code. Hockley (2008) examined the picture superiority effect using an associative recognition memory paradigm, where subjects were asked to study lists containing random pairs of words and pairs of drawings, and later were required to discriminate between intact and rearranged pairs of words and pictures. The result revealed an advantage for pictures over words using intact picture pairs, which supported the idea that benefits of pictorial stimuli originate from the encoding stage. Furthermore, in order to compare the difference between within- and cross-modality effect in RM, Sternberg, Radeborg, & Hedman (1995) investigated the congruency of item modality (word vs. picture) between studying and testing phase. The result demonstrated better recognition and faster processing speed when test items were congruent in presentation modality between study and test, compared with cross-modality items, which was consistent with the TAP effect identified in RM studies. This unique link, or facilitation, between the encoding and the retrieval stage in RM was highlighted by the multi-process theory in PM, and further demonstrated that the relationship between the underlying processes during the PM encoding phase and the PM retrieval phase could benefit either spontaneous or effortful processing. The current PM experiment used a cross-modality design, and the observed superiority effect for items presented as pictures in the 'lighter item' task were actually presented as words during the preceding 'odd one out' procedure (i.e. the PM encoding stage). This seems to contradict the findings in RM (Hockley, 2008) by revealing that items in word format during the PM encoding stage result in better performance in the subsequent 'lighter item' task, as well as in PM target detection. Nevertheless, it is important to point out that subjects were required to work out the PM target by themselves mentally, which meant that the PM targets were never physically presented to subjects during the

PM encoding stage. It is therefore possible that t PM targets were stored in a conceptual format instead of either in word or picture format. As a result, the superior performance for pictures over words observed in the 'lighter item' task, as well as PM detection, was that pictures carry a lot more information than words in general, and are often processed faster and more accurately than words. Furthermore, information in the non-verbal format could be more easily for subjects to imagine than information in verbal format, and was more concrete and easier to process. Lastly, we should emphasise that in the current PM experiment, we did not deliberately try to match the modality of experimental materials (word vs. picture) in terms of its memorability, but to use a cross-modality design along with an additional 'odd one out' procedure to control for the TAP and the repetitive priming effects to PM performance. Our results suggested that delayed intentions can be encoded in a format-nonspecific way, and highlighted the dominance of the pictorial stimuli during PM retrieval stage in a cross-modality PM study.

fMRI effect in the lighter item task

The fMRI part of the result could be divided into two parts, the 'lighter item' task that was associated with PM retrieval and the 'odd one out' procedure that was involved with PM encoding. First, in the 'lighter item' task, when contrasting the 'OG-only' and the 'PM' blocks, the analysis revealed a standard PM network, where the 'PM' vs. 'OG-only' contrast demonstrated activation in the lateral rPFC region, and the 'OG-only' vs. 'PM' contrast showed stronger activation in the medial rPFC region (Burgess et al., 2001; 2003). Given that the current PM experiment implemented several novel manipulations including cross-modality design, self-initiated PM intention, single PM target block design, and relatively short retention period (15 seconds maximum), it is critical to first confirm that the current paradigm elicited a PM-like network that demonstrated a standard lateral vs. medial dissociation in the rPFC region.

The comparison between the ‘exemplar’ and the ‘category’ conditions was analysed in two approaches, a boxcar modelling for the sustained ‘block’ effect, and a delta-function modelling for the transient ‘trial’ effect. The comparison of the sustained brain activities between blocks including PM targets varying in specificity showed that the ‘category’ condition elicited stronger activations in the posterior region including the fusiform gyrus and occipital regions, compared with the ‘exemplar’ condition. The observed activations in the posterior regions suggested an enhanced bottom-up mechanism was involved with maintaining an unspecified PM intention, compared with maintaining a specified PM intention. This was inconsistent with the finding revealed in McDaniel et al. (2013), which identified stronger sustained activity in the left anterior PFC region when processing non-focal PM, and this has been interpreted as a regulation of top-down attentional mechanism in PM tests (Burgess et al., 2011). In the multi-process theory, non-focal PM cues require sustained attentional control to maintain a constant recognition process in order to identify the item as a PM target, but the identification of focal PM cues can be accomplished by spontaneous, effortless retrieval process. There were several possibilities relating to the novel manipulations we implemented in the current PM experiment that might lead to this opposite finding to McDaniel et al. (2013). First, the relatively short block duration might limit any potential observation of ‘sustained’ PM effect, which by definition, would be more prominent for a longer maintenance period. Second, the single PM target and the constant shifts between detecting exemplar and category PM targets between blocks made subjects unable to engage in a PM-retrieval mode (Guynn, 2003; Lepage, Ghaffar, Nyberg, & Tulving, 2000) that favoured a non-focal PM condition evident by the PPI analysis in McDaniel et al. (2013). Third, repetition priming was shown to associate with reduction in neural activation in several brain regions, and was referred as the ‘response suppression’ (Schacter and Buckner, 1998). It is possible that the cross-modality design in current PM experiments disabled the suppression effect observed in repetition priming, and subsequently led to a bottom-up, stimulus-driven effect in the posterior lobes, including right fusiform gyrus. Importantly, interaction between the ‘type’ and the ‘modality’ factors identified activation in the same right fusiform gyrus was stronger in the ‘category’ than in the ‘exemplar’ condition only when using picture stimuli, but not word stimuli. This format-sensitive effect was consistent with the finding showing that the right fusiform gyrus is more sensitive to visual form alterations about objects (Marsolek, 1999; Simons, Koutstaal, Prince, Wagner, & Schacter, 2003).

The comparison on the transient brain activities between PM targets trials varying in specificity revealed stronger activations in the left BA46 region when contrasting the ‘category’ condition to the ‘exemplar’ condition. In McDaniel et al. (2013), when processing both focal and non-focal PM targets, the result identified equivalent PM-related activity in ventral brain regions. The observed activation in ventral brain regions was interpreted as an engagement of bottom-up attentional shift and detection of salient target stimuli (Cabeza Ciaramelli, Olson, & Moscovitch, 2008), which supported the multi-process theory proposing that the retrieval of focal PM intentions relies more on bottom-up processes. In the current PM experiment, after controlling for the TAP and repetitive priming effect to PM performance, we proposed that correct identification to category PM targets, relative to exemplar PM targets, involved a top-down mechanism in the left dorsolateral PFC region located in BA46. As revealed by Frith et al. (1991), the dorsolateral PFC region is activated when making actions with higher degrees of ‘response space’, which accompany willed, open-ended decisions. Successful detection of category PM targets, compared with detecting exemplar PM targets, requires a top-down evaluation of possible associative links between the encoded PM intention and the expected PM target. In other words, subjects are required to make more open-ended decisions, or utilise a bigger ‘response space’, in order to successfully detect potential PM targets in the ‘category’ condition than in the ‘exemplar’ condition, and willed action regulated by the dorsolateral PFC region evident by Frith et al. (1991). The frontal regulation observed in our study further suggests that when the TAP and repetitive priming effects, which presumably were more related to stimulus-driven, bottom-up process, are controlled, it was a top-down regulatory mechanism that differentiated potential PM targets varying in specificity. We should emphasise that, as with the contradictory findings in the behavioural part of the result, we did not argue against the core idea of the multi-process theory, but demonstrated different brain networks that associated with processing PM intentions varied in specificity instead. Last, we identified a ‘type’ x ‘modality’ interaction in the right fusiform gyrus. Follow-up analysis showed that sustained activity associated with maintaining PM intentions was stronger in the category vs. exemplar contrast only for picture stimuli, but not for word stimuli. This differentiation between modality suggested that, without the benefits from the TAP and repetitive priming effects, subjects selectively engaged in non-verbal aspect of the information. Under the circumstance where one is maintaining unspecified PM intentions (e.g., the category condition), a higher demand on the stimulus-driven mechanism may be required, and this facilitates processing of items in pictorial format.

fMRI effect during the odd one out procedure

We further analysed brain activity during the ‘odd one out’ procedure, and focused on examining the effect of PM encoding and categorisation, or the odd one out process itself. During the PM coding stage, stronger activations in posterior regions including lingual gyrus and bilateral fusiform gyrus were found when comparing the ‘PM’ blocks to the ‘OG-only’ blocks collapsing the ‘type’ and the ‘modality’ factors. Previous neuropsychological studies have identified that the lingual gyrus plays an important role in both visual and word processing. For example, Machielsen, Rombouts, Barkhof, Scheltens, & Witter (2000) used fMRI to investigate the brain regions linked to encoding the images for later recognition, and the lingual gyrus was one of the many structures that were involved with memorizing the images. Critically, in a recognition test a few weeks later, similar activation in lingual gyrus was found during the recollection process. Furthermore, the lingual gyrus also was evident to involve with naming stimuli (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 1995), and activated during logical processing for future events (Brunet, Sarfati, Hardy-Bayle, & Decety, 2000). In the current PM experiment, subjects were required to memorise PM targets in the ‘PM’ blocks, but not in the ‘OG-only’ blocks. As a result, an additional encoding process was involved, and the purpose for this memorisation was to identify future PM targets. The observed lingual/fusiform gyrus activation during PM encoding was also found during the subsequent PM retrieval stage when comparing the ‘category’ condition to the ‘exemplar’ condition. This highlighted the potential role of the lingual gyrus in the current PM experiment, which included a naming process of the encoded target, evaluation of future events logically, and a reactivation during subsequent retrieval of unspecified PM targets. It is important to note that, no activations were found anywhere when comparing between blocks using pictures and words. This null finding implied that, during the PM encoding, the memorisation process of PM targets did not rely more on either verbal or non-verbal aspect of the information. This supported our speculation that the inconsistent finding to the picture superiority effect originated from encoding stage (Hockley, 2008), where the neural activity during PM encoding of PM targets relied on a conceptual, format-unspecific way. Comparison between the blocks including PM targets varying in specificity identified stronger activation in the dorsomedial PFC region when comparing the ‘category’ condition with the ‘exemplar’ condition. The observed activation was part of a proactive brain network in Bar (2009), which proposed that human brain is a proactive system that continuously generates predictions for anticipating relevant future events. This foresight was achieved by an analogical link that focused on predictions via associative activation of representations. Therefore, the predictive brain could rely on existing scripts in memory, or previously imagined experiences, when foreseeing future situations. In the current PM experiment, subjects needed to generate a higher level of prediction between the encoded and the anticipated PM target in the ‘category’ condition during the ‘odd one out’ procedure. On the other hand, the prediction between the encoded and the anticipated PM target in the ‘exemplar’ condition had a specified linkage, and subsequently required a lower level of proactive thinking. In addition, the odd one out procedure could be divided into an initial analogical process that first identifies the similarity between the two items belonging to the same category before building an associative link between the encoded and the anticipated PM target in a predictive way. As mentioned in the introduction section, the dorsomedial PFC region was linked to functions including making analogical inferences (Volle, Gilbert, Benoit, & Burgess, 2010), detection of similarity between dissimilar targets (Pothos, 2005), comparison between expectation (Summerfield et al., 2006), and envisage farsighted decisions (Benoit, Gilbert, & Burgess, 2011). The observed stronger dorsomedial PFC activation in the category vs. exemplar contrast during PM encoding suggested that this region is also involved with the formation of more predictive future intentions. Last, analysis of the categorisation process during the 'odd one out' procedure showed widespread activations across the anterior and the posterior regions, including occipital lobe and frontal lobe when contrasting the 'PM' blocks to the 'OG-only' blocks. This indicated that odd one out for meaningful items elicited both bottom-up and top-down neural networks. By contrast, when comparing the 'OG-only' blocks to the 'PM' blocks, stronger activations were identified in the right parietal and the medial rPFC regions. The medial rPFC activation located in BA10 was consistent with the 'rostral PFC attentional gateway' proposed by Burgess, Dumontheil, & Gilbert (2007), where the medial rPFC region was found to activate when focusing on stimulus-oriented (SO) thoughts compared with engaging in stimulus-independent (SI) processing. In the current PM experiment, when doing the odd one out, the 'OG-only' blocks required subjects to process either lines or letters, which could be accomplished by viewing physical features of the items. In the 'PM' blocks, on the other hand, subjects needed to identify pictures of objects and meaningful words, which involved more effort to process, and therefore relied on processing semantic information. It is possible that the observed medial rPFC activation when comparing the 'OG-only' blocks with the 'PM' blocks was related to higher level of SO processing, and was consistent with the proposed gateway role of the rPFC region in Burgess, Dumontheil, & Gilbert (2007).

To sum up, the aim of the current PM experiment was to investigate the cognitive processes to maintain and detect PM intentions varying in specificity. We designed a novel PM paradigm that implemented several novel manipulations including cross-modality design, single PM target block design, self-initiated PM intention, to control for the potential TAP and repetitive priming effects to PM performance. The behavioural part of the results demonstrated a possible format-sensitive differentiation between processing PM intentions varied in specificity. The functional neuroimaging results further revealed a dorsolateral PFC activation that related to regulation of a more open-ended category PM targets, compared with pre-determined exemplar PM targets during PM retrieval. In the PM encoding stage, we identified a dorsomedial PFC activation that was associated with more proactive future predicting mechanism when encoding an unspecified PM intention, compared with encoding a specified PM intention. Together these results highlighted the functional roles that different PFC sub-regions play in PM performance with varying levels of specificity.

Chapter 9. Creativity and the PFC region

9.1 Creativity, culture, and the PFC region

Creativity is an ability that involves various aspects of high-level cognition and is essential to a range of human behaviours, from trivial daily matters like coming up with a new way to make everyday lives easier, to extraordinary achievements that significantly improve human society. A critical difference between this complex function and other cognitive processes (e.g., attention, memory, language) is in the range of definitions amongst individuals. When it comes to creative experience, everyone has their own idea of what creativity describes, and personal experiences could vary fundamentally, e.g., having an ‘aha’ moment, finding new solutions to routine tasks, or sophisticated art creation. In order to study this complex mental function experimentally, it is essential to have an agreed definition of this mental ability and to design reliable measurement tools to examine the underlying cognitive processes it involves. Previous psychological studies have proposed that to elicit some acts that are considered creative requires generating outcomes that are both novel (original), and useful (appropriate) (Sternberg and Lubart, 1999; Plucker and Makel, 2010; Runco and Jaeger, 2012). This definition, although simplified, provides scope and opportunity to develop psychometry to measure observable creative behaviours, and investigate the neural correlates in human brain associated with the experimental variables. To capture the cardinal features of creativity, many theoretical frameworks have been proposed. However, they have yielded inconsistent findings, with little agreement so far (Fink, Benedek, Grabner, Staudt, & Neubauer, 2007; Arden, Chavez, Grazioplene, & Jung, 2010; Dietrich and Kanso, 2010; Sawyer, 2011).

For instance, one of the earliest studies of creativity was Guilford (1950), who assessed the ability to generate multiple solutions to open-ended problems without an absolute right or wrong answer, a function later referred as divergent-thinking. In order to quantified these open-ended answers experimentally, several carefully defined criteria were introduced, including fluency (e.g., the quantity of responses), originality (e.g., the degree of uncommon of responses), flexibility (e.g., the number of different categories of responses), and complexity (e.g., the enrichment of responses). Other theoretical frameworks measured the verbal aspect of creativity, and focused on examining the ability to combine words that were remotely related in a semantic context, e.g., the Remote Associates test (Mednick, Mednick, & Mednick, 1964). Dietrich and Kanso (2010) reviewed six functional imaging studies implemented divergent-thinking tests to subjects and highlighted the critical role that the PFC region plays in this kind of creativity paradigm. On the other hand, when reviewing previous neuropsychological experiments using the Remote Associates test, it was the anterior cingulate cortex, as well as the superior temporal gyrus, that were identified as being involved with semantic aspect of creative thoughts. This implies that creativity tests measuring different aspects of creative actions might associate with distinct cortical regions in the PFC area. Other reviews of neuroimaging and electrophysiological studies have also pinpointed the importance of the PFC region in creative thinking, but have not specifically highlighted the link between different aspect of creativity and different PFC sub-regions (Arden et al., 2010; Fink and Benedek, 2013).

As a form of higher-level human cognition, creative acts require various kinds of processes, for example, mental flexibility, verbal fluency, working memory, planning and organising ideas, and incidentally, these cognitive functions are all shown to involve the PFC region (Carlsson, Wendt, & Risberg, 2000; Zeki, 2001;

Dietrich, 2004; Bogousslavsky, 2005; Changeux, 2005; Ward, 2007). It is possible that these various kinds of cognitive processes and their links to the PFC region have profound contributions to creative behaviours measured by different psychometrical tests. Gonen-Yaacovi, Cruz de Souza, Levy, Urbanski, Josse, & Volle (2013) conducted a meta-analysis to statistically test the global and distinct associations between different PFC sub-regions and different experimental paradigms requiring creativity. In order to specify the potential process-specific PFC sub-regions, the experiments included in the meta-analysis were first categorised into two separate dimensions, the core 'nature' of creativity tests (combination vs. unusual generation tests), and the 'stimuli' used for creativity tests (verbal vs. non-verbal). As defined by Gonen-Yaacovi and colleagues, the 'combination' kind of creativity tests involved developing associations between remote elements of information in order to generate a new outcome, whereas the 'unusual generation' kind of creativity tests focused on examining the level of fluency, originality, flexibility, and complexity of the uncommon ideas (Guilford, 1950). Coordinate-based meta-analysis using Activation Likelihood Estimation (ALE) method first identified that, in general, many PFC sub-regions including the caudal lateral PFC, the medial and lateral rostral PFC region are implicated in creativity experiments and these were included for the analyses. When comparing between the core 'nature', the 'combination' type of creativity tests, compared with the 'unusual generation' kind of creativity tests, showed stronger activations in the left lateral rostral PFC (in BA10) and the bilateral inferior frontal gyrus (in BA45, 46). In the reverse 'unusual generation' vs. 'combination' contrast, the left middle frontal gyrus (in BA9) was found to be more activated. This comparison between the 'nature' of creativity tests identified enhanced recruitment of the lateral rostral PFC region in the 'combination vs. unusual generation' contrast, which revealed processes that enabling integration of multiple solutions based on remote association or related similarity. This was consistent with the proposed hierarchical organisation of the PFC functions along a dimension of progressively higher degree of abstraction (Christoff et al., 2001; Hampshire et al., 2010; Krawczyk, McClelland, Donovan, Tillman, & Mcguire, 2010). Enhanced dorsolateral PFC activation in BA9 in the ‘unusual generation vs. combination’ contrast, on the other hand, was in line with the idea of a fronto-parietal network that has its functional role in working memory, monitoring and random generation of actions (Frith et al., 1991; Rowe, Hughes, Eckstein, & Owen, 2008). This implied a potential explanation that creative thinking requiring unusual generation, compared with combining different semantic ideas, involved implementing a greater room to generate free choices of responses. Therefore, the enhanced BA9 activation highlighted the importance of these spontaneous willed actions for ‘unusual generation’ kinds of creativity tests in relative to other creativity paradigms. When comparing the type of stimuli used in the various creativity tests, the verbal tests elicited higher activations mainly in the bilateral PFC regions (in BA8, 9, 10, 44, 46, 47) than the non-verbal tests, and the reverse contrast demonstrated enhanced neural activity in the left middle frontal gyrus (in BA9). Although dissociations between verbal vs. non-verbal information in the lateral caudal PFC region are frequently reported (Goldman-Rakic, 1987; Sakai and Passingham, 2003; Volle et al., 2008), due to the mixed stimuli used in the non-verbal creativity tests (visual, spatial, music), it was not possible to interpret the enhanced left rostral PFC activation in the non-verbal vs. verbal contrast. Together these findings support the view that creativity involves distinct cognitive processes along different dimensions, and confirms that different creativity tests make different demands on functions that associate with different PFC sub-regions. As a result, given that creativity is a complex function that different measurements would activate different neural networks, it is reasonable to have inconsistent findings between different theoretical frameworks, or even individuals with different backgrounds. However, investigation on the topic is relatively scarce.

Previous studies have demonstrated that experience has a profound effect in sculpturing brain structure. For example, increased regional brain size is found in functionally associated cortical regions accompanying superior behavioural performance in a wide range of cognitive domains including second language acquisition (Golestani, Molko, Dehaene, Lebihan, & Pallier, 2007; Green, Crinion, & Price, 2007), spatial navigation (Maquire et al., 2000), and music ability (Gaser & Schlaug, 2003). A classic example, for instance, comes from sustained practice in juggling, where regional brain volume is increased through behavioural training (Draganski et al., 2004; Boyke, Driemeyer, Gaser, Buchel, & May, 2008). These studies posited a promising notion that experience can affect brain structure, and show the plasticity in structural changes morphometrically. When considering the exposure to sustained practice or effect on a longitudinal scale, it is possible to suspect that a more influential factor, e.g., the environment, or the culture we live in, might show significant effects upon human function and brain structure. A prevalent distinction between cultures suggests that Easterners (e.g., Asians) and Westerners (e.g., UK, US) show different cognitive processing originating from their own merits of collectivism (people who focus more on the significance of cohesion with social groups) versus individualism (people who emphasis more on personal liberty and desire self-reliance by opposing external interference) philosophies within the Eastern and the Western societies respectively (Nisbett and Masuda, 2003). Some researchers have proposed that it is the manner of information processing that leads to cross-cultural differences, where Asians consider matters holistically and the Westerners viewed things analytically (Park and Gutches, 2002; Nisbett and

Miyamoto, 2005). Functionally, empirical evidence comes from neuroscientific studies like eyetracking data (Chua, Boland, & Nisbett, 2005) and fMRI techniques (Han and Northoff, 2008) that have demonstrated that cultural differences play an important role in daily cognitive functions. Structurally, two imaging studies have examined morphological differences in brain structure between the Easterners and Westerners, and both highlighted the significance of language and its linked cortical areas in cultural difference (Green et al., 2007; Kochunov et al., 2003). Their results identified increased tissue in multiple structures including left inferior frontal cortex, which was interpreted as the requirement for using Chinese, as compared with using English. Chee, Zheng, Goh,Park, & Sutton (2011) extended this cross-cultural effect in structural-based studies by investigating differences in brain structure as a function of age between Asians (Singaporean) and Westerners (Americans), as well as the environmental effects in young (mean age=21 yrs) and older adults (mean age=64 yrs). The results showed that young Westerners had higher cortical thickness and larger volume in multiple brain regions including the bilateral inferior frontal gyrus (BA10, 11, 45, 47) on the lateral surface, and the bilateral superior frontal gyrus (BA9, 10) on the medial surface. The observed difference in cortical thickness between younger subjects was not significant in older subjects. These findings suggest that individuals from the Eastern and the Western societies may have distinct behavioural patterns in a range of cognitions that are reflected in differences in cortical structure in the PFC region.

People from Eastern and the Western countries are thought to have distinct values that originate from the environment they experience. In particular, there is a common perception that the Eastern and the Western cultures have different creative behaviours, and much of the difference across cultures seems to be the relative weight placed on the two main aspects of creativity: novelty and usefulness

(Sternberg and Lubart, 1999). Inn the West, “creativity” emphasises originality-based phenomena (i.e. novelty) relating perhaps to individualism, whereas Eastern notions of creativity are more focused on a connection to the practical realm with the aim of maintaining interpersonal harmony (Villalba, 2008). One of the theories explaining this difference was proposed by Nisbett and colleagues (Peng and Nisbett, 1999; Nisbett, Peng, Choi, & Norenzayam, 2001; Nisbett and Masuda, 2003), who argued that the Eastern and the Western cultures have distinct biases in information processing. In the Western societies, individualistic and self-centred characteristics are encouraged, and people tend to process central objects and organise information in an analytical way. In contrast, East Asian countries have a rich historical background that focuses on their collectivist heritage, and people tend to consider themselves as part of a larger whole by biasing more on contextual information. In order to measure the difference between this individualism vs. collectivism, two types of self-construal, independent and interdependent self-perception, were proposed to conceptualise this distinction (Markus and Kitayama, 1991). Although everyone possesses both kinds of self-construal, individuals tend to use one more than the other to guide their behaviour in fitting within their culture. The independent self-construal is defined as a bounded, unitary, stable self that is separate from social context, where people put emphasis more on the independent self by considering themselves unique and distinct from others, and pursuit the goals they value (Singelis, 1994). The interdependent self-construal is defined as a flexible, variable self that focuses on the connection with others, where people with interdependent self-concern with enacting appropriate behaviours and maintain harmony with others in order to pursuit belongingness (Singelis, 1994). These characteristics made interdependent individuals more likely to act in accordance with other’s expectation, instead of following their internal wishes or personal values. As a result, it seems necessary to consider this cultural modulator in higher-level cognition like creativity, especially when both functional and structural differences relating to the PFC region have been identified between the two cultures (Han and Northoff, 2008; Chee et al., 2011).

In the current study, we compared creativity between two countries, using Taiwan as the sample Eastern country and the UK as the sample Western country. To create a culture-free comparison, we used creativity tests that required minimum verbal content. Based on the categorisation of creativity tests by Gonen-Yaacovi et al. (2013), we included the Alternative Uses test (Guilford, 1967) as a measurement for ‘unusual generation’ kind of creativity. Given that the ‘combination’ kind of creativity tests usually involves semantic processing, e.g., the Remote Associates test (Mednick et al., 1964), we did not included any measurement in this category. In non-verbal dimension, we included the Design fluency test (Jones-Gotman and Milner (1977), as a measurement for creative thinking that required minimum amount of semantic processing. Incidentally, a meta-analysis using the coordinate-based ALE method in Gonen-Yoaacovi et al. (2013) showed that similar regions in the left BA9 were activated in the ‘unusual generation’ vs. ‘combination’ contrast, as in the ‘non-verbal’ vs. ‘verbal’ contrast. This prompted us to examine if there is a function-structure link between this PFC sub-region and the creativity function it supported. In Chee et al. (2011), structural-based analysis was conducted to examine the structural difference between cultures using cognitive matched young and old adults from Singaporeans and Americans. Using a vector machine-based classification with a threshold at accuracy > 65% identified several cortical regions was able to differentiate Singaporean and Americans, including bilateral inferior PFC region located closely to BA9 region (see illustration of the identified inferior PFC region in Figure 9.1). As the classic juggle experiment demonstrated, experience can sculpt brain structure and human function, and increased cortical volumes can be associated with improvement with practicing on purpose (Draganski et al., 2004). Therefore, we hypothesised that individuals from Taiwan and the UK would show difference in creative performances. Moreover, previous theoretical frameworks discussing creativity proposed that a creative act involves generating ideas that are both novel (original) and useful (appropriate). These two dimensions describing creative behaviours are in some ways consistent with the distinct cultural values between the Western and the Eastern societies in individualism and collectivism, respectively (Villalba, 2008). The two psychometric tests we used for cross-cultural study, the Design fluency test and the Alternative Uses test, could be viewed as creativity measurements that weigh more on the novelty and the usefulness aspects of creativity, respectively. For example, to obtain higher score in the Design fluency test, subjects need to generate as many as drawings as they can within a fixed period. Importantly, the generated design should be something that is not nameable or the fragments of existing items, and as a result this requires subjects to use creative thinking that relies more on novelty or originality. In contrast, the Alternative Uses test, as the name suggested, requires subjects to come up with as many uncommon uses of common objects as possible within time limit. Critically, although uncommon, the generated uses for the particular item should be applicable or practical in some ways, and subsequently can be used to measure creative ability on the useful or practical side. Given that the difference on cultural philosophies described earlier, we suspect that the Westerners would focus more on the novelty (or originality) aspect of creativity because of individualism, where individualists tend to exercise their liberty and the highlight the importance of free wills. This kind of personal belief supposes to benefit more on the novel (or original) side of creative thinking. On the other hand, the Easterners would emphasis more on the usefulness (practicality) aspect of creativity due to collectivism, where collectivists cherish the importance of being a group member and therefore prioritise the goal of the group. This characteristic might encourage creative thinking to put more effort on the side that potentially affects others, or its usefulness. As a result, we hypothesised that the Easterners and the Westerners would demonstrate distinct pattern of performance in the two creative tests we used. We have three hypotheses for this cross-cultural study on creativity. First, we hypothesised that the Easterners and the Westerners would show distinct performance on the two creative tests that associated with the PFC region (Gonen-Yoncovi et al., 2013). Second, based on the potential mapping between cross-cultural values (individualism vs. collectivism) and the two kinds of self-construal (independent vs. interdependent), we hypothesised that the Westerners would show higher level of independent self-construal, whereas the Easterners would demonstrate higher level of interdependent self-construal using the Self-construal Scale (Singelis, 1994). Third, we suspect the two creativity tests we included have different weightings on the two proposed aspects of creativity, where the Design fluency test measures more the novelty part of creativity, and the Alternative Uses test focuses more on the usefulness part of creativity. Based on previous cross-cultural studies suggesting the two cultures have distinct values, we hypothesised that the British subjects would have better score in the Design fluency test (relies more on novelty), whilst Taiwanese would generate more creative ideas in the Alternative Uses test (focuses more on usefulness). To complete this cross-cultural study, a PhD student (a native Taiwanese, Hsuan-Chen Wu), as the examiner, travelled to Taiwan and recruited a group of young Taiwanese adults. The Taiwanese group was required to administer a Chinese version of creativity questionnaire including a range of psychometry. The examiner then return to the UK and recruited a group of young British adults, and the equivalent English version of creativity questionnaire was administered to them. It is necessary to recruit native Taiwanese in Taiwan because (a) Taiwanese students in the UK will be a self-selecting sample, and (b) they have already been exposed to Western behavioural and cognitive norms. The creativity questionnaire from both groups of subjects were then scored by four ‘blind’ raters, two native Taiwanese and two native British, who were not given any background information regarding to the purpose of the study. More detailed information of the creativity questionnaire is summarised in the methods section.

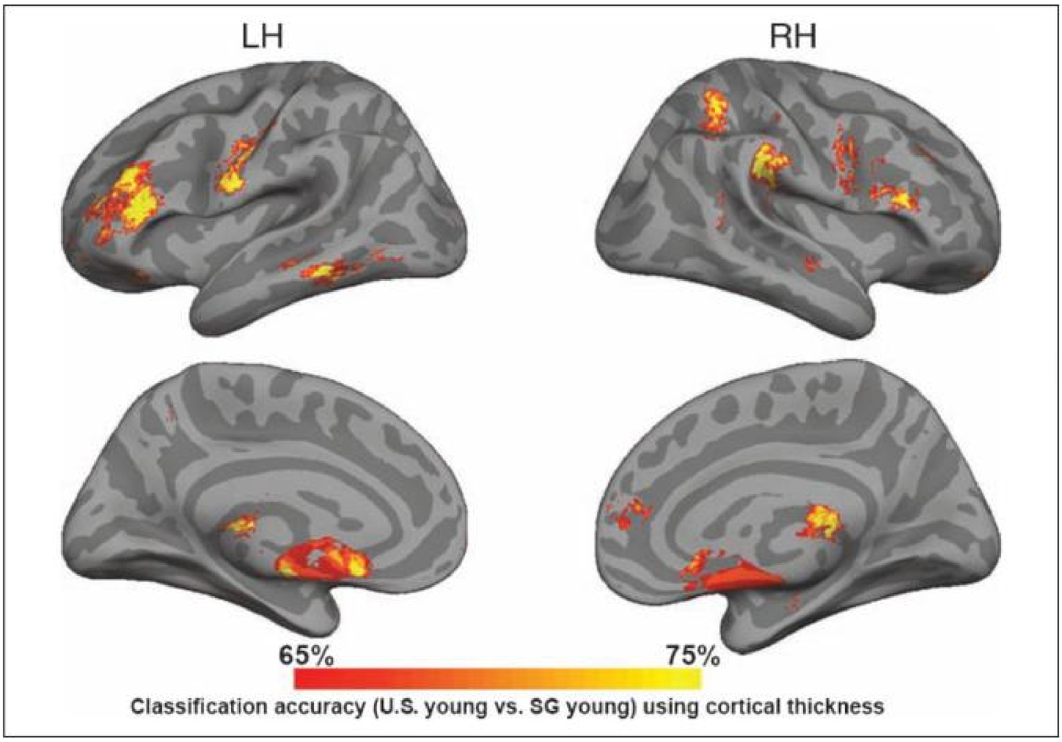


Figure 9.1. Illustration of the bilateral inferior PFC region in BA9 that ables to differentiate Singaporean and Americans in Chee et al. (2011).

9.2 Methods

Subjects

Twenty-two native Taiwanese adults (15 male) and seventeen native British adults (11 male) were recruited to administer the same creativity questionnaire in the version of their native language. The Taiwanese subjects were recruited from the subject database in the Institute of Cognitive Neuroscience, Central University, Taiwan, and the British group were recruited from the subject database at the Institute of Cognitive Neuroscience, University College London, United Kingdom. Both groups of subjects had no histories of hearing, visual, motor impairments or neurological disorders. All subjects were required to complete a personal information section including gender, age, language, discipline studied, family income, whether they had visited other countries more than a month, familiarity to the other culture, and self-assessment of one's own creativity in a range of 1 (the lowest) to 5 (the highest). The average age of the Taiwanese group (mean=29 yrs) was significantly higher than the British group (mean=24.1 yrs; $t(38)=2.405$, $p=0.021$). No significant differences were found between the self-assessed familiarity to the other culture (Taiwanese: 3 out of 5, British: 2.68 out of 5; $t(38)=1.158$, $p=0.254$). Importantly, self-assessment of one's own creativity revealed that the British group (mean=3.4 out of 6) rated themselves significantly higher than the Taiwanese group (mean=2.8 out of 5; $t(38)=2.521$, $p=0.016$).

Design and procedure

The creativity measurement tool consisted of seven sections. The first section required subjects to provide some personal information. The second section titled ‘reasoning ability’ involved testing the subject’s general intelligence using the Raven’s Advanced Progressive Matrices Test (APM, Raven, Court, & Raven, 1988). The third section titled ‘your design fluency on creativity’ included a ‘free’ condition and a ‘fixed’ condition adapted from the Design fluency test (Jones-Gotman and Milner, 1977). All subjects were required to finish the ‘free’ condition first then the ‘fixed’ condition. In the fourth section, called ‘the ways you show your creativity’, subjects needed to complete the Alternative Uses test (Guilford, 1967) by generating uses for three common items in the following order: brick, newspaper, and pen. The fifth section was called ‘your definition of the concept of creativity’, and subjects were asked to choose ten of the total twenty listed adjectives that they considered related to creativity. The sixth section was labelled ‘applications of creativity’, which involved asking subjects to rate 24 listed actions varying in level of creativity (low vs. high) along twelve different disciplines according to three dimensions: creativity, novelty, and usefulness. For example, repair an electronic device (lower level of creativity) vs. build an electronic device from junk or waste (higher level of creativity) in the engineering discipline. The eighth section, which was titled ‘your understanding of yourself’, included 28 statements where subjects needed to evaluate themselves on a 6-point scale, in order to control for the potential neutral responses and forced subjects to choose a side. All subjects were administered the creativity questionnaire in the same order, and only the third and the fourth section had a time constraint, whilst the other sections were self-paced. The creativity investigation took each subject approximately 50 minutes to finish.

Psychomety and scoring

Raters for the Design fluency test and the Alternative Uses test

Two native Taiwanese and two native British ‘blind’ raters were recruited to score the creativity questionnaire. The four raters were one male Taiwanese aged 28 years old majoring in psychology, one female Taiwanese aged 23 years old majoring in architecture, one male British aged 25 years old majoring in psychology, and one female British aged 25 years old majoring in medicine. All the raters read the scoring criteria sheet first, and then were trained by the examiner to ensure their capability to give reliable scores using the same criterion. The raters were not informed of the purpose of the rating (for cross-cultural study), and rated all the questionnaires (no.1 to no. 39) in the same order.

Raven’s APM (Raven, Court, & Raven, 1988)

The Ravens Progressive Matrices were originally developed to assess higher level mental ability, which consisted of a series of progressively more difficult items that required subjects to choose which piece (from eight options) that best completed a pattern series. We used the Ravens Advanced Progressive Matrices test (APM, Raven, Court, & Raven, 1988) set A, that uses non-verbal materials, which enables measuring general intelligence for populations where the contribution of language should be minimized (e.g., subjects for whom English is not their first language). This lower demand of culture loading of Raven’s APM made it an ideal measurement for estimating general intelligence between the Taiwanese and the British groups. Superior performance required no special knowledge of vocabulary because all testing items were geometric matrices, but still demonstrated probably the purest measure of analytical fluid intelligence (Carpenter, Just, and Shell, 1990). Subjects were told that the test was for measuring reasoning ability, and their task was to identify the figure that was to right ‘shape’ to fill the space. The number of errors made was an index of estimated general intelligence.

Design fluency test (Jones-Gotman and Milner, 1977)

Jones-Gotman and Milner (1977) developed the Design fluency test that used visuospatial method to measure the ability to utilise one’s own strategy to maximise the production of responses and avoid repetition at the same time. The analogous verbal fluency test (Benton, 1968; Milner, 1964) has proved to be sensitive to frontal lobe dysfunction. The Design fluency test was administered by oral instruction, and subjects were encouraged to draw as many different designs as they could within time limits. In the ‘free’ condition of the test, subjects were required to draw different non-verbal designs on a paper in 5 minutes. The restrictions for the designs followed the original design fluency test (Jones-Gotman & Milner, 1977), which included: a) drawing nameable objects or fragments of those is not allowed; b) drawing existed geometric objects is not allowed; c) scribbling is not allowed, because they usually look similar (see Figure 9.2(a), for illustration of the English version). After finishing the ‘free’ condition, subjects were told that they needed to complete another drawing session, the ‘fixed’ condition, with other additional restrictions on the top of the ‘free’ condition. The further rule limited the drawings to four segments: a) a circle would be count as one line, as would a gentle curve; and b) a sharp angle would make two lines, as would a steep twist (see Figure 9.2(b), for illustration of the English version). The examiner encouraged subjects to make as many different designs as possible within 4 minutes, and emphasised that the designs in this condition had to consist of exactly four lines without ambiguity. Before administering the test, subjects were asked to read all the instructions by themselves first, and the examiner explained all the restrictions again. During the drawing period, subjects were allowed to ask questions or request elaboration of the rules once, and the examiner would point out subject's mistake for the first time. For subjects claiming to be unable to make any designs, the examiner would give verbal encouragement once, but still required subjects to wait until the full time elapsed.

(a)

Creativity Questionnaire

Section 3: your design fluency on creativity

In the following section, please be prepared to make some drawings.

(1) Free condition

We would like you to make as many different drawings as you can in 5 minutes.

However, there are some restrictions you should know before you start.

a) Drawing nameable objects, or even fragments of those is not allowed.

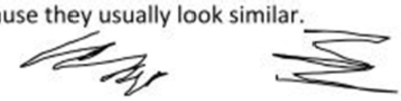
Ex. Drawing an apple, or its stem is not allowed; drawing a bird, or its wings is not allowed.

b) Drawing existed geometric objects is not allowed.

Ex. Drawing a circle, a triangle, rectangle ... is not allowed.

c) Scribbling is not allowed, because they usually look similar.

Ex.



Please start your drawing now.

(b)

Creativity Questionnaire

(2) Fixed condition

In this condition, we would like you to make as many different drawings as you can in 4 minutes.

Howeer, this time each drawing have to consist of exactly four lines without ambiguity.

There are some rules and restrictions you should know before you start.

a) A circle would be count as one line, as would a gentle curve.

b) A sharp angle would make two lines, as would a steep twist.

c) Drawing nameable objects, or even fragments of those is not allowed.

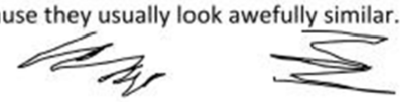
Ex. Drawing an apple, or its stem is not allowed; drawing a bird, or its wings is not allowed.

d) Drawing existed geometric objects is not allowed.

Ex. Drawing a circle, a triangle, rectangle ... is not allowed.

e) Scribbling is not allowed, because they usually look awefully similar.

Ex.



Please start your drawing now.

Figure 9.2. The English version of the Design fluency test included in the creativity questionnaire, where panel (a) shows the introduction for the free condition and panel (b) demonstrates the introduction for the fixed condition.

For the scoring of the Design fluency test, the four raters needed to identify the total number of designs, the number of erroneous designs that did not follow the restrictions, and the number of valid designs. Furthermore, the raters were required to rate the valid designs as a whole on four different aspects: creativity, similarity, originality and complexity (Guilford, 1950). The score was made on a 6-point scale, where1 indicated that the rater strongly disagreed that the design showed creativity/similarity/originality/complexity, and 6 meant that the rater strongly agreed that the designs demonstrated creativity/similarity/originality/complexity.

Alternative uses test (Guilford, 1967)

The Alternative Uses test was designed by J.P. Guilford, the founder of modern creativity research, as part of his Structure of Intellect, which provided simple measurement for evaluating divergent thinking ability, or spontaneous flexibility (Guilford, 1967). In the Alternative Uses test, subjects were asked to generate uncommon uses for common objects in a given amount of time. This paper-based test provided a psychometric approach to measure the divergent thinking part of creative ideas. Subjects were instructed to show their creativity by thinking of as many uses as possible for several common objects. An example of uses for a ‘paper clip’ was listed as an example to subjects, in order to demonstrate potential directions of creative thinking (see Figure 9.3). The examiner emphasised that any wild ideas were welcomed and no restrictions were set in this section, except for the 3 minute limitation of responding. The three common objects were ‘brick’, ‘newspaper’, and ‘pen’, and were presented one by one in different pages to prevent pre-exposure of the next item.

For the scoring of the Alternative Uses test, the raters were asked to identify the total number of uses, and further count the number of uncommon ones separately. In addition, the raters needed to give scores based on the creativity, similarity, originality, and practicality of the uncommon uses generated by each subject on a 6-point scale.

Creativity Questionnaire

Section 4: your ways to show your creativity

We would like you to think of as many uses as possible for some common objects.
For example, here's a sample brainstorm for uses of 'paper clip':

a) hold paper together
b) can be a substitute for cufflinks
c) can be earrings, if you want to
d) it looks like mini-trombone to me
e) thing you can use to push emergency restart button on the router cuz it's thin
f) keep headphones from getting tangled up
g) can be a bookmark

As you can see, any wild idea or any linkage you can think of related the target item are accepted.
There is basically no restrictions or limitations in this section. It is all about your creativity.
You have three minutes for each object, and here is the first object you need to work on:

Figure 9.3. The introduction of the Alternative Uses test included in the English version creativity questionnaire, where several examples on the uses of 'paper clip' were given to subjects.

Self-construal scale (Singelis, 1994)

Markus and Kitayama (1991) proposed that different self-images have influences on an individual's cognition, emotion, and motivation, and the distinction between independent and interdependent self-construal could be a possible explanation for cultural differences in various kinds of cognition from lower-level perception to higher-level motivation. As a result, we focused on examining how subjects viewed themselves and its difference across cultures, given that the two cultures were shown to have differences between the two kinds of self-construal.

The self-construal scale focused on measuring two aspects of self-concepts, independent and interdependent, and subjects were required to give evaluation on themselves to 28 statements using a 6-point scale.

9.3 Result of the creativity psychometry

Because of the significant differences in age between the two groups, all the following analyses were conducted in ANCOVA model where the effect of age was partialed out from the data. The group factor (Taiwanese vs. British) was included as a fixed factor, and the measurements in each test of the creative questionnaire were included as dependent variables in ANCOVA (see Table 9.1, for summary).

Table 9.1. The results of the Raven's APM, the Design fluency, the Alternative Uses test included in the creativity questionnaire.

Test	Condition	Measurement	British		Taiwanese		Significance
			mean	SD	mean	SD	
Raven's APM							
		Errors	0.88	1.50	1	1.09	p=0.436
Design fluency test							
	Free condition						
		Total designs	9.58	6.18	4.77	2.81	p=0.006 *
		Errors	0.85	0.73	1.10	0.86	p=0.503
		Valid designs	8.70	6.08	3.67	2.98	p=0.004 *
		Creativity	3.77	1.17	3.15	1.42	p=0.361
		Similarity	3.51	0.85	3.54	1.25	p=0.831
		Originality	3.70	1.04	3.21	1.27	p=0.383
		Complexity	3.80	1.03	2.90	1.23	p=0.068
	Fixed condition						
		Total designs	15.23	7.23	9.95	4.56	p=0.025 *
		Errors	2.22	1.38	2.64	1.48	p=0.208
		Valid designs	13.01	6.86	7.30	4.42	p=0.009 *
		Creativity	2.94	0.99	2.77	1.17	p=0.916
		Similarity	3.80	0.75	3.57	0.96	p=0.310
		Originality	2.69	0.62	2.43	1.10	p=0.580
		Complexity	2.35	0.74	2.23	0.94	p=0.951
Alternative Uses test							
	Brick						
		Total uses	7.60	1.84	6.90	1.95	p=0.332
		Uncommon uses	3.69	1.42	3.43	1.32	p=0.721
		Creativity	2.94	0.73	2.82	0.84	p=0.952
		Similarity	3.11	0.71	2.88	0.71	p=0.037 *
		Originality	2.97	0.74	2.79	0.88	p=0.797
		Practicality	4.85	0.48	4.62	0.26	p=0.006 *
	Newspaper						
		Total uses	9.05	2.25	8.13	2.66	p=0.269
		Uncommon uses	4.11	1.36	4.02	1.37	p=0.973
		Creativity	2.66	0.54	2.67	0.75	p=0.715
		Similarity	3.04	1.00	2.71	0.60	p=0.202
		Originality	2.64	0.51	2.64	0.68	p=0.816
		Practicality	4.61	0.43	4.70	0.44	p=0.503
	Pen						
		Total uses	7.82	2.72	7.36	2.77	p=0.620
		Uncommon uses	3.75	2.06	3.90	1.83	p=0.703
		Creativity	2.94	1.26	3.06	1.24	p=0.498
		Similarity	2.97	1.00	2.61	0.88	p=0.250
		Originality	2.89	1.13	2.90	1.17	p=0.694
		Practicality	4.55	0.66	4.29	1.14	p=0.404

* Independent t test significance p<0.05

Raven’s APM

ANCOVA on the number of errors in Raven’s APM did not find a significant difference between groups ($F(1,36)=0.622$, $p=0.436$).

Design fluency test

In the ‘free’ condition, the British group generated significantly more designs ($F(1,36)=8.706$, $p=0.006$), as well as significantly more valid designs ($F(1,36)=9.420$, $p=0.004$), than the Taiwanese group (see Figure 9.4, for some of the designs). No other significant effects of group were found in any other measurements in the ‘free’ condition. In the ‘fixed’ condition, ANCOVA found that the number of generated designs ($F(1,36)=5.455$, $p=0.025$), as well as the number of valid designs ($F(1,36)=7.610$, $p=0.009$), were significantly higher in the British group than in the Taiwanese group. No significant effects of group were found in the ratings in the ‘fixed’ condition.

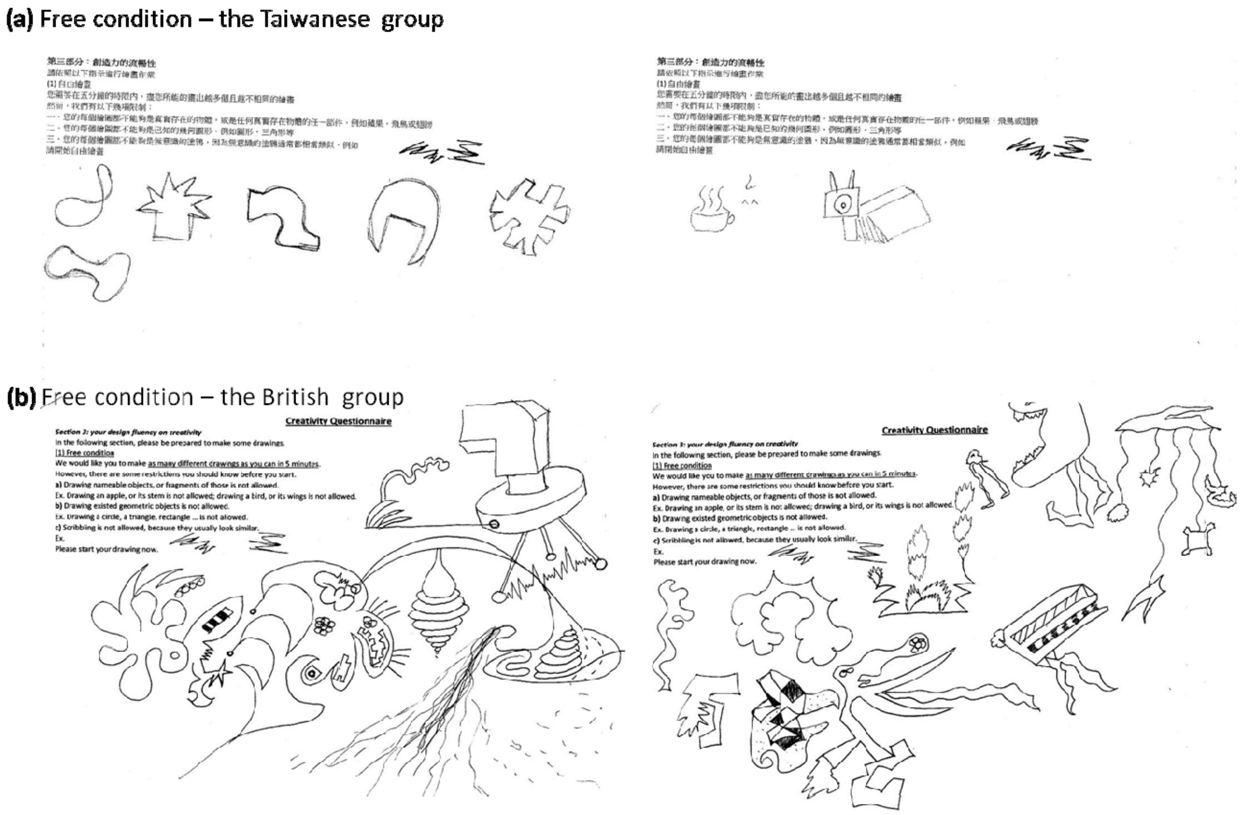


Figure 9.4. The generated designs from two Taiwanese subjects (in panel a) and two British subjects (in panel b) in the free condition of the Design fluency test included in the creativity questionnaire.

<u>Alternative Uses test</u>

For the ‘brick’ item, the raters gave the British group significantly higher scores on similarity ($F(1,36)=4.715$, $p=0.037$) and higher scores on practicality ($F(1,36)=8.408$, $p=0.006$). No other significant group differences were found between the number of total uses, the number of uncommon uses, and other ratings including creativity, similarity, originality, and practicality to the ‘newspaper’ and the ‘pen’ items.

Self-construal scale

ANCOVA revealed that the British group did not show significantly higher independent self-construal than the Taiwanese group ($F(1,36)=0.046$, $p=0.832$). Similarly, the Taiwanese group did not demonstrate significantly higher interdependent self-construal than the British group ($F(1,36)=1.223$, $p=0.276$).

Supplementary analysis

In order to statistically examine if the two cultures showed superiority on different aspects of creativity (novelty vs. usefulness), we first examine if the test scores from the two creativity tests measures distinct component of creative thinking. However, the subject number of the current study was too few (17 British vs. 22 Taiwanese), and the number of measurements was also too few to conduct a reasonable data extraction analysis (e.g., principal component analysis). As a result, we used Spearman's rank-order correlation analysis to investigate the relationship between test measurements within and between the Design fluency and the Alternative Uses test. In the Design fluency test, we included the number of valid designs in the 'free' and the 'fixed' conditions, given that invalid designs (e.g., drawing nameable objects, or repetitive designs) did not reflect the 'novelty' aspect of creativity. In the Alternative Uses test, we included the number of uncommon uses of the three items separately, because generating common uses of common objects did not require any creativity. Spearman correlation analysis revealed a positive significant correlation between the number of valid designs between the two conditions in the Design fluency test, but these two measures were not significantly correlated with any measures in the Alternative Uses test. On the other hand, positive significant correlations were found between the number of uncommon uses of the three items in the Alternative Uses test, and these three measures were not significantly correlated with any measures in the Design fluency test (see Table.9.2 for summary). Based on the distinct inter-correlation of measures between the two creativity tests, we further summed the five test scores in the Design fluency and the Alternative Uses tests separately to form a representative test score for each test. Next we inputted the summed scores from the Design fluency test (the DF score) and the Alternative Uses test (the AU score) into repeated measures ANOVA, with group (Taiwanese vs. British) as between-subject factor, test (AU vs. DF) as within-subject factor, and age as covariate of non-interest. Repeated measures ANOVA revealed a significant main effect of group ($F(1,36)=9.460$, $p=0.004$), where the British group had significantly higher test scores overall than the Taiwanese group. No significant main effect of test was found ($F(1,36)=0.344$, $p=0.561$). Critically, a significant group x test interaction was found ($F(1,36)=8.283$, $p=0.007$), and follow-up analysis showed that the British group had significantly higher DF test scores , but not in the AU test scores (see Figure 9.5).

Table 9.2. The relationships between variables from the Design fluency and the Alternative Uses tests using Spearman's rank-order correlation analysis, where ** indicates p<0.01.

	DF item (free)	DF item (fixed)	AU item (brick)	AU item (newspaper)	AU item (pen)
DF item (free)		0.554 **	-0.200	0.171	0.029
DF item (fixed)			-0.015	0.059	0.014
AU item (brick)				0.534 **	0.693 **
AU item (newspaper)					0.726 **
AU item (pen)					

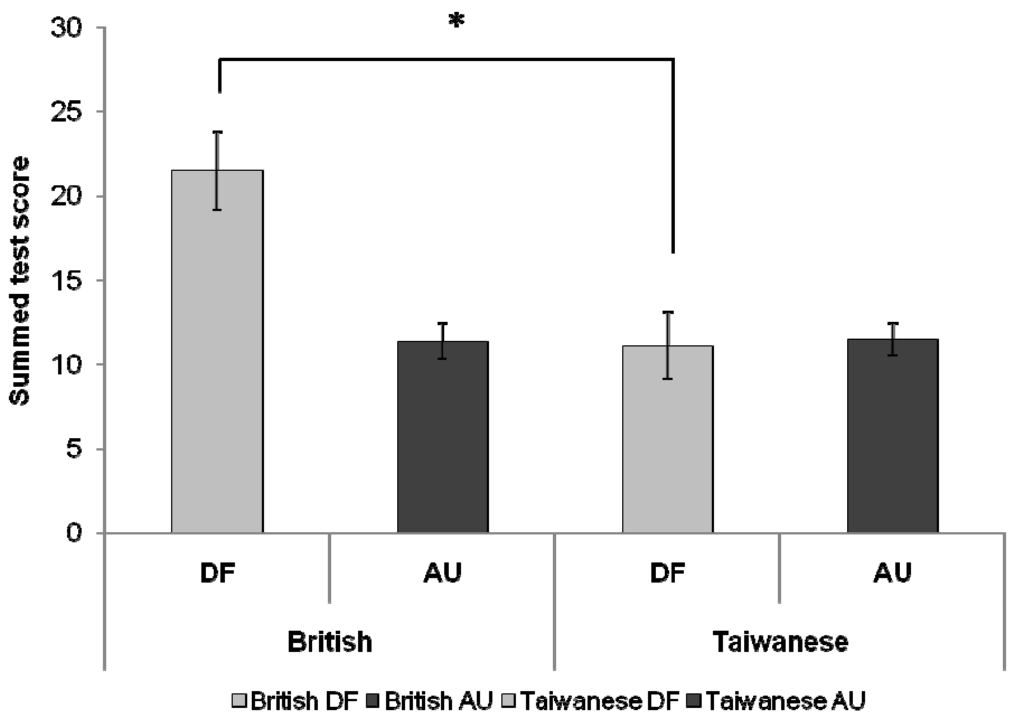


Figure 9.5. The group x test interaction revealed by repeated measures ANOVA, which shows the British subjects have significantly higher scores in the Design

fluency test, but the difference between groups is not significant in the Alternative Uses test.

9.4 Discussion of the creativity questionnaire

In this study, we used a cross-cultural approach to investigate different aspects of creativity that supposedly supported by different PFC regions, given that creativity is a complex function that involves various kinds of cognition, and meta-analysis demonstrated both shared and specific activations in distinct PFC sub-regions support different creativity tests (Gonen-Yoaacovi et al., 2013). We used a cultural neuroscience approach by comparing creative behaviours between a group of Taiwanese and a group of British young adults. Demographically, the average age was significantly higher in the Taiwanese group than the British group. Although the age was not perfectly matched between groups, other background information including gender ratio, visited the other country or not, familiarity to the other culture, did not show significant effect of group (Chi-square test all $p>0.05$). Importantly, the number of errors in the Raven's APM did not show significant difference between groups, which indicated that the subjects from two cultures have comparable analytical fluid intelligence. Any observed differences in the creativity questionnaire could not be explained by these factors. It is important to note that, the British group rated themselves with significantly higher creativity than the Taiwanese group did, even after the effect of age was partialled out. It was suggested that the Westerners were more inclined to attribute human behaviours to their internal dispositions predominately, whilst the Easterners tended to explain their behaviours in an interpersonal context (Choi, Nisbett, & Norenzayan, 1999). In section five of the creativity questionnaire, we asked subjects to select the adjectives that related to creativity based on their own definition. All the seventeen British subjects chose ‘talented’ as one of the adjectives that related to creativity, whereas only sixteen out of the total twenty-two Taiwanese subjects chose ‘talented’ (Chi-square test p=0.019, two tailed). This simple difference in definition to creativity may suggest that British subjects show a higher tendency to attribute creative ability as a kind of personal disposition than Taiwanese subjects. Together with the significantly higher self-ratings of creativity, these results were consistent with the cross-cultural different suggested by Choi et al. (1999), and further demonstrated cross-cultural differences could be identified even without implementing well-established psychometric measurements, but manifest using simple self-report questionnaire.

Next, we analysed the rating scores of the two classic creativity tests, the Design fluency test (Jones-Gotman and Milner, 1977) and the Alternative Uses test (Guilford, 1967), and focused on the difference between groups. In the Design fluency test, the British group made significantly more total number of designs and more valid designs in both ‘free’ and ‘fixed’ conditions. On the other hand, in the Alternative Uses test, the British group generated more total uses than the Taiwanese group for all three items, as well as more uncommon uses for two of the three items, but none of these group differences was significant. Previous cultural and cognitive framework discussed that possibility that Asians are more likely to fixate on contextual information and Westerners tend to fixate on central objects using eye-tracking technique (Chua, Boland, & Nisbett, 2005). Similar evidence also suggests cultural differences in processing facial stimuli (Blais, Jack, Scheepers, Fiset, & Caldara, 2008), and the functional imaging method has also demonstrated that East Asians and Westerners involve distinct neural networks in ventral visual cortex (Gutchess, Welsh, Boduroglu, & Park, 2006). The current study proposed a possible cross-cultural effect on creativity, which is a higher-level cognition that is evident to associate with the PFC region.

In order to examine the possible association between cultural values and creativity, analysis on the Self-construal scale (Singelis, 1994) first found that our Taiwanese subjects reported themselves to have higher interdependent self-construal score, yet not significant, than British subjects, whilst British subjects did not show higher independent self-construal than Taiwanese subjects did. This higher interdependent characteristics amongst the Easterners than the Westerners supported the individualistic vs. collectivist hypothesis and was consistent with our second hypothesis that there is a mapping between self-construal (independent vs. interdependent) and social values. Furthermore, this difference in self-assessment of personal traits provides a potential scope to explain the distinction between cultures observed in other measurements of the creativity questionnaire. In order to test the potential dissociation between the performance in different creativity tests (the Design fluency and the Alternative Uses test) and different cultures (Taiwan vs. the UK), we first conducted Spearman's rank-order correlation analysis to examine if the two creativity tests measured distinct creative behaviours. The result showed that the measures in each test were positively correlated with each other (all $p<0.01$), but not significantly correlated with measures between tests. Based on the difference in the requirement for the two creativity tests, the Design fluency test did not emphasise on any practicality issue of the generated designs but focused on its novelty, yet the Alternative Uses test asked subjects to come up with unusual uses of common objects, which innately required their practicality. The result of Spearman's rank-order correlation analysis therefore suggested a possible differentiation of the two creativity tests, where the Design fluency test specified the importance of the novelty aspect of creativity, and Alternative Uses test highlighted the usefulness aspect of creative thoughts. Critically, repeated measures ANOVA using the summed test scores revealed a significant group x test interaction, showing the British group had significantly higher performance only in the DF test score but the difference was not significant in the AU test score, compared with the Taiwanese group. This interaction indicated that the observed superior performance between groups in creative behaviour was only evident in creative behaviours focused more on the novelty aspect but comparable on the usefulness side. Together with the result identified in the self-construal scale, it is possible that the interaction between test and cultures on creative behaviours was wired in different societal values. As proposed by Markus and Kitayama (1991), the Western societies encourage more individualistic and self-centred characteristics, compared with the East Asian culture, which focused more on the collectivist culture to view them as part of a larger whole. This suggested a weighting scheme between self-reflection and considering other's thoughts might modulate the creative behaviours that emphasise on either novelty or usefulness, which are potentially linked to the independent and interdependent self-construal in the British and the Taiwanese groups respectively. For example, social cognition processes, including self-reference, making inference of other's mental states, empathy for other's emotional states, and social rejection, are involved with both common and distinct neural activities in different PFC sub-regions (see Liebermann, 2007 for review). Han and Ma (2014) summarised 35 fMRI studies investigating cultural effects on human cognition and conducted a whole-brain meta-analysis to identify the potential cross-cultural differences in brain activation associated with social cognitive, social affective and non-social tasks. The result found that East Asians had stronger activity in the dorsomedial PFC and lateral PFC regions when administering social cognitive tasks, and showed enhanced activation in the ACC, ventromedial PFC in

Westerners. Social affective tasks were associated with higher activation in the right dorsolateral PFC in Asians but greater activity in the left insula in Westerners. These distinct neural network between cultures highlighted that the East Asian culture demonstrated stronger neural activity in brain regions relating to making inference of other's mind (e.g., dorsomedial PFC), whereas the Western culture revealed increased activation in brain regions associated with self-reference processing (e.g., ventromedial PFC). An important implication of this meta-analysis is the influence from socio-cultural environment to neural activity, which shows culturally sensitive neural processes that relate to different social behaviours between individualism (the West) and collectivism (the East). Therefore, it seems reasonable to suspect that the cultural values that emphasise different social cognitions might affect the underlying neural mechanisms associated with different PFC sub-regions. Subsequently, this profound cultural effect also contributes to other higher-level cognitions, like creativity, and can lead to dissociation on creativity measurements weight on aspects relating to others (usefulness, practicality) or not (novelty, uniqueness).

To sum up, this creativity study proposed a fruitful direction on comparing cross-cultural difference on higher-level cognition which was evident to be supported by the PFC region, and was consistent with the view that practices and environmental experiences might sculpt functions. However, due to the relatively small groups of students recruited from both countries, there were many potential reasons to observe the differences on creative thinking here. This includes factors originate from subjects (e.g., the discipline they studied), the educational background (e.g., Taiwanese education systems do not reward students being creative as in the UK), or even the psychometry implemented (e.g., the creativity tests included are all invented by the Westerners, and it might not be surprising to find the Westerners perform better in most of them). It is important to note that all the

Taiwanese and the British subjects acquired for the current study have structural brain scans, and this could be useful for further brain-based measures (e.g., voxel-based morphometry). More data and resources are required to investigate the function-structure relationship on cross-cultural effect and particular brain structure, which refer to creativity and the PFC region, in this case. Therefore the intention of this study is to serve as a pilot run leading to a more substantial collaboration between the UK and Taiwan, or other Eastern countries. This work might bring together cognitive neuroscientist who is interested in how the PFC region supports creativity, and researchers who have academic background in sociology, business, or education. Studies on human creativity is fundamentally important, given that it is commonly enunciated by business leaders that encouraging innovation is at the heart of economic success. However, it is not clear that this can be achieved at present, since the necessary psychometric tools that are required to measure creativity do not exist. This study seems to be a seed study aims at starting to bring the methodologies of cognitive neuroscience to bear upon this issue, with a view to developing new psychometric instruments in the future. Nevertheless, it is important to note that this cultural framework targets at measuring structure-function links in the PFC region does not indicate that culture is the only factor that sculpts functional difference between the East and the West. The effect of culture could be viewed as a developmental trajectory that influences culturally specific functional organisation of human brain in very sophisticated way.

Chapter 10. General discussion of the thesis

Converging evidence from different methodologies including various kinds of neuroimaging techniques and different subject pathologies has demonstrated functional specialisation within the PFC region. It is now possible and necessary to examine the established function-structure links by comparing findings acquired from different experimental approaches. The current thesis could be divided into three major sections, the PFC battery section, the prospective memory section, and the creativity investigation section. In each section, we use hypothesis-testing approach to first identify the higher-level cognitions supported by different PFC sub-regions, and then designed new psychometric tests and implemented new approaches, to test the relationship between particular functions, and in most cases a specific PFC sub-region that was putatively involved with them.

In the PFC battery chapters, the four new psychometric tests are as simple as playing some gambling on imaginary money, deciding which item was more similar to a reference, watching some videos that involved some conversations, and reading some comics that might violate social norms. However, the performances of a large group of TD subjects, VBM findings from the TD sub-group, and comparisons between ASD subjects are extremely fruitful in understanding the underlying constructs and brain regions that support them. All four new psychometric tests from the PFC battery broadly confirm the function-structure relationships between varying kinds of performances and their associated PFC sub-regions established by previous functional imaging studies. This provides strong supporting evidence for the functional role of the given PFC sub-region of interest in each PFC battery test, and further indicates a potential link between the regional GM volume and the elicited rCBF activity observed in contrast comparisons. Nevertheless, a common inference drawn from functional imaging studies is that when a cognitive process A occurs, a particular brain region X is activated. However, Poldrack (2006) pinpointed a reverse inference fallacy, where reasoning goes backwards from the presence of brain activation to the engagement of a particular cognitive function. As mentioned in earlier chapters, no cognitive function could be ascribed to any cortical region exclusively, nor is a particular brain region activated solely by one cognitive process (e.g., the specificity issue of the meta-analysis method). The observed function-structure relationships in the PFC battery chapters are established by the links between behavioural variables and regional GM size in the PFC region. It is therefore easier to make inferences based on simple logic such as 'bigger GM size in region X is associated with better behavioural variables measuring function A'. When mapping the identified GM clusters that associate with different variables across different PFC battery tests, it appears that some of the neural correlates are located in similar regions, e.g., the dorsomedial PFC region (see Figure 10.1). Spearman rank-order correlation showed that most of the variables that significantly correlated with the GM volume in the dorsomedial PFC region are also significantly inter-correlated with each other in a positive direction (see Table 10.1). Critically, principal component analysis of the TD group revealed that the G_repetitiveness factor (including G_wrep, G_lrep) and the M_high+lowmentalizing factor (including M_highgroupacc, M_lowdyadacc, M_lowgroupacc) are identified as loading on the same component. A potential explanation of these overlapping GM clusters that associate with variables in risky decision-making and social cognition might relate to stereotype behaviours. A stereotyping network was proposed to involve with the encoding and storage of stereotype concepts, the selection and activation of these concepts into working memory and their application in behaviours (Amodio, 2014).

The dorsomedial PFC region, as part of the network, was suggested to support the formation of impression about other people, which required mentalizing to consider other's perspective and motives, a process that engaged in theory of mind. This underlying mechanism is similar during risky decision-making, where people would generate impression to particular items as well, e.g., this person might give me a hard time vs. this option might make me loss money, and these impression would lead to a stereotype-like behaviour to make judgments in a rigid mannerism. On the other hand, another PFC sub-region that is identified to be associated with various PFC battery variables is the lateral OFC region. As Figure 10.2 depicted, the location of the GM clusters in the lateral OFC region that correlate with variables measuring different cognitions is more wide spread than the GM clusters in the dorsomedial PFC region. More importantly, it appears that the lateral OFC region is more 'versatile' in a functional way than the dorsomedial PFC region. The regional volume of different GM clusters in this particular PFC sub-region is correlated with variables measuring a wide range of mental abilities including risky decision-making (risk rate, repetitiveness), cognitive bias (framing effect), reverse learning processes (consistency score), and faux pas detection (overall faux pas accuracy). Spearman rank-order correlation showed that, compared with the dorsomedial PFC region, most of the variables that significantly correlated with the GM volume in the lateral OFC region do not show significant inter-correlation with each other (see Table 10.2). This is consistent with the view of the multiple-demand (MD) pattern of frontal and parietal activity that diversely associates with different cognitive functions measured by a various kinds of methods (Duncan, 2006; 2010). Incidentally, the set of regions in the PFC region of the MD system include the posterior part of the inferior frontal sulcus, the anterior insula and adjacent frontal operculum, and the pre-supplementary motor area extending to dorsal anterior cingulated cortex (see

Figure 1 in Duncan, 2010). Furthermore, similar activity pattern in the PFC region could be also identified in standard test of fluid intelligence, and this general (or *g*) factor is proposed to contribute to performance across tests measuring different cognitions (Duncan et al., 2000; Bishop, Fossella, Croucher, & Duncan, 2008). These findings using functional imaging technique suggest a pattern of brain activation is associated with multiple kinds of cognitive demands, and significant increased activity in the right OFC (peak MNI: 36, 36, -15) region is found during tasks with high-*g* involvement compared with matched low-*g* control tasks (Bishop et al., 2008). Therefore, the converging results from behavioural and VBM analyses in the PFC battery chapters demonstrate a promising direction of using a reverse-engineering (but not reverse *inference*) method to investigate the function-structure relationship using structural-based techniques. Given that cytoarchitectonic differences have been identified both between lateral and medial sub-regions of rostral PFC (Petrides & Pandya, 1999) and between rostral and caudal sub-regions within rostral PFC (Carmichael & Price, 1994), functional specialisation of the rostral PFC region (BA10) has also been identified. For example, Gilbert et al. (2006) conducted a meta-analysis of 104 functional imaging studies and revealed functional variation along a rostral-caudal axis of the rostral PFC region. Nevertheless, in Gilbert et al. (2006), the activation peaks from different psychological paradigms were located close to one another, e.g., the peak activation of studies involving mentalizing tests was reliably caudal to those from other kinds of studies, and the mean difference along the y coordinates between different categories was only 4 mm with substantial overlap between two distributions. As depicted in Figure 10.1, structural-based analysis with higher spatial resolution than functional imaging studies also shows both overlapping and non-overlapping GM clusters in the dorsomedial PFC region. Despite the overwhelming evidence suggesting functional specialisation of the PFC region, it is still debatable to what extent this segregation exists, e.g., different PFC sub-regions evidently link to different cognitions, yet these seemingly different cognitions might share some overlapping mechanisms that associate with similar PFC sub-regions. A new methodology combining findings from different techniques should be a promising future direction to answer this question.

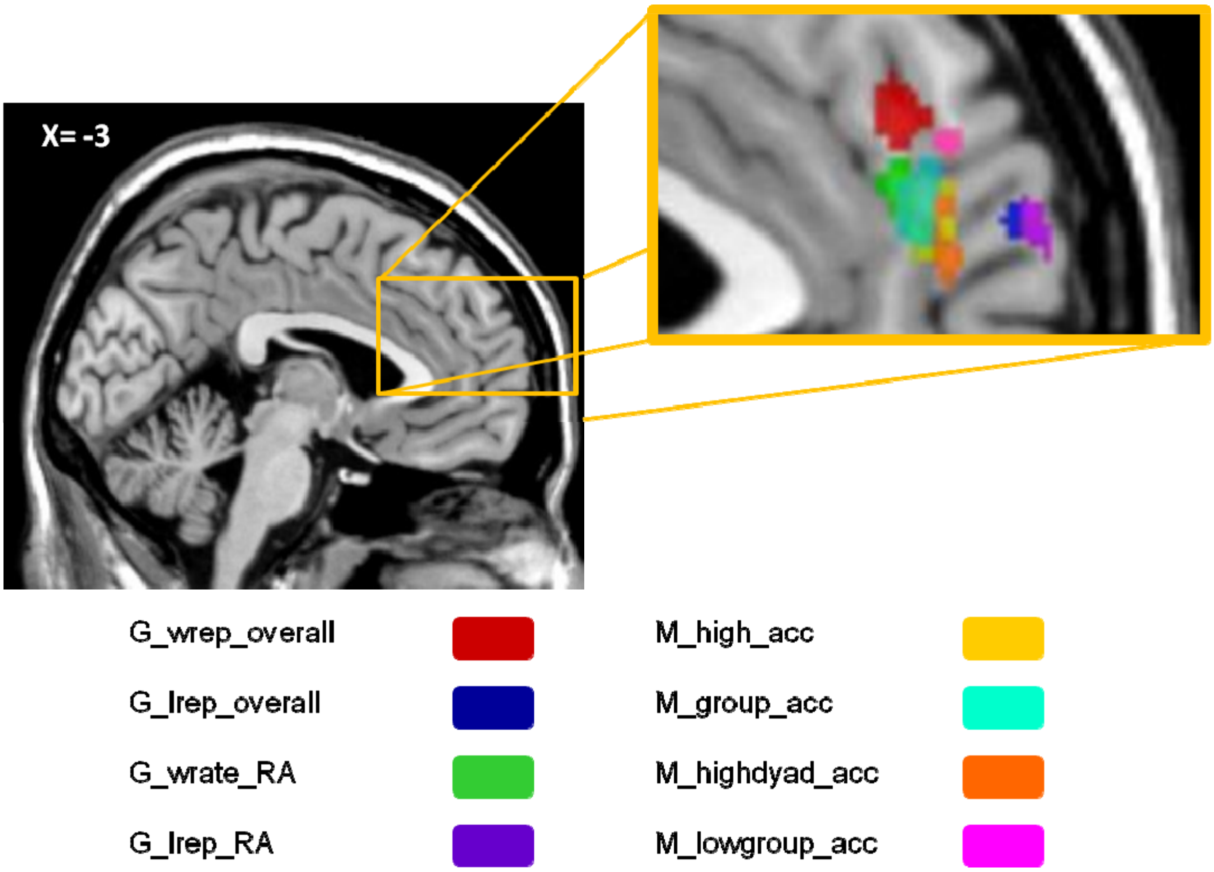


Figure 10.1. All the GM clusters are overlaid on a MNI152 template using MRI croN software. G_wrep_overall: the overall repetitiveness in the win condition of the gambling test; G_lrep_overall: the overall repetitiveness in the loss condition of the gambling test; G_wrate_RA: the risk rate to RA trials in the win condition of the gambling test; G_lrep_RA: the repetitiveness to RA trials in the loss condition of the gambling test; M_high_acc: the accuracy for high-mentalizing videos in the video mentalizing test; M_group_acc: the accuracy for group conversation videos in the video mentalizing test; M_highdyad_acc: the accuracy for high-mentalizing dyad videos in the video mentalizing test; M_lowgroup_acc: the accuracy for low-mentalizing group videos in the video mentalizing test.

Table 10.1. The correlations between all the PFC battery variables that significantly correlate with the dorsomedial PFC region. All the relationships that have a p value <0.05 using spearman's rank-order correlation analysis are labelled 'v' in the table.

	The gambling test				The video mentalizing test			
	G_wrep_overall	G_lrep_overall	G_wrate_RA	G_lrep_RA	M_high_acc	M_group_acc	M_highdyad_acc	M_lowgroup_acc
G_wrep_overall		**v**		**v**		**v**		**v**
G_lrep_overall	**v**			**v**	**v**	**v**	**v**	**v**
G_wrate_RA								
G_lrep_RA	**v**	**v**			**v**	**v**	**v**	**v**
M_high_acc		**v**		**v**		**v**	**v**	**v**
M_group_acc	**v**	**v**		**v**	**v**			**v**
M_highdyad_acc		**v**		**v**	**v**			
M_lowgroup_acc	**v**	**v**		**v**	**v**	**v**		

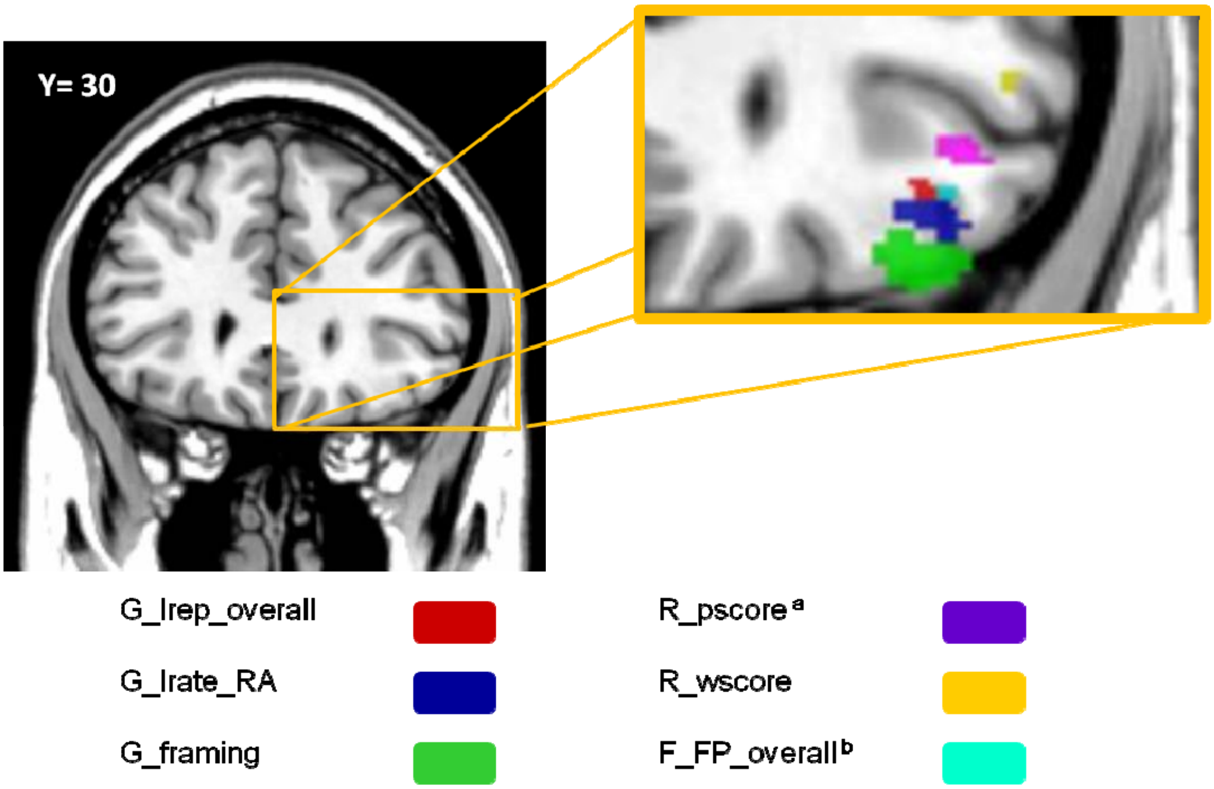


Figure 10.2. All the GM clusters are overlaid on a MNI152 template using MRI croN software. G_lrep_overall: the overall repetitiveness in the loss condition of the gambling test; G_lrate_RA: risk rate to RA trials in the loss condition of the gambling test; G_framing: the size of framing effect of the gambling test; R_pscore: consistency score in the personality condition of the referential judgment test; R_wscore: consistency score in the weight condition of the referential judgment test; F_FP_overall: the overall accuracy for the faux pas and the non-faux pas cartoons of the cartoon faux pas test. [a] p=0.051 at FWE-corrected threshold. [b] p=0.052 at FWE-corrected threshold.

Table 10.2. The correlations between all the PFC battery variables that significantly correlate with the lateral OFC region. All the relationships that have a p value <0.05 using spearman's rank-order correlation analysis are labelled 'v' in the table.

	The gambling test			The referential judgment test		The cartoon faux pas test
	G_Irep_overall	G_Irate_RA	G_framing	R_pscore	R_wscore	F_FP_overall
G_Irep_overall		**v**				**v**
G_Irate_RA	**v**		**v**			**v**
G_framing		**v**				
R_pscore						
R_wscore						
F_FP_overall	**v**	**v**				

In the PM chapter, on the basis of a classic PM paradigm including a prospective memory task on the top of a baseline ongoing task, we implemented new approaches to examine the cognitive mechanism involved when processing PM targets that vary in specificity. The two experimental variables we manipulated, the 'type' of PM targets and the 'modality' of stimuli, measured the effect of top-down regulation and bottom-up processing respectively. The fMRI part of the result demonstrates that PM, as a mental ability involves predicting future events, requires both activations in the rostral PFC region, as well as posterior brain activities in the occipital region. Nevertheless, it is important to note that we do not find any significant effect between 'type' of PM targets in the behavioural part of the result. Instead, we observed strong effect between 'modality' of stimuli. However, when plotting the behavioural performance from each subject between 'type' and 'modality', the behavioural data actually demonstrate remarkable individual differences on the effect of 'type' and little or no difference on the effect of 'modality'. As illustrated in Figure 10.3, subjects are consistently making more accurate PM detections and shorter response times to pictures than to words, and show distinct superiority between exemplar targets and category targets. This indicates that different subjects implement different strategies when identifying and responding to PM targets that vary in specificity, compared to a robust picture superiority effect when processing stimuli differ in format. These behavioural and functional imaging results first demonstrate collaboration between 'perceptual' and 'executive' parts of cognition in prospective memory, where we remember to execute what we perceive and we perceive what we remember to execute. Furthermore, the distinct response pattern between 'type' and 'modality' may suggest a meta-cognitive process that regulates the 'executive' part of the PM network, which is consistent with the strategic difference in implementing reminders for PM intention offloading as observed in Gilbert (2015).

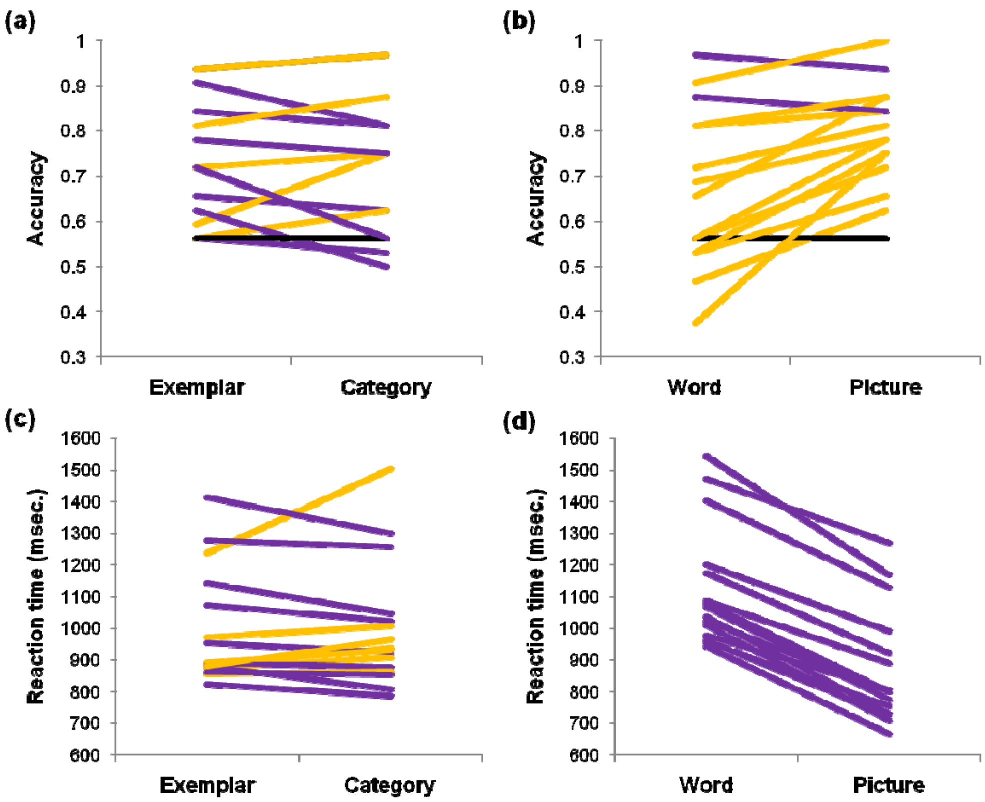


Figure 10.3. Behavioural data from every subject in the PM experiment. Panel (a) and (b) shows individual response in accuracy, where panel (c) and (d) shows individual response in reaction time. For lines in yellow colour: subjects having higher accuracy and longer reaction times in the exemplar vs. category and the word vs. picture comparisons. For lines in purple colour: subjects having lower accuracy and faster reaction times in the exemplar vs. category and the word vs. picture comparisons. For lines in black colour indicate equal values in the comparison.

In the creativity questionnaire section, we demonstrated dissociation between different aspects of creative behaviours and different cultures. This between-population individual difference further demonstrates that the ‘typical’ performance in one population might be ‘atypical’ in another population. Although current creativity studies do not provide any direct evidence on the causal relationship between cultural difference and higher-level cognition supported by the PFC region, recent studies in the field of cultural neuroscience reveal convincing evidence that cultural values have a profound effect on human functions. For example, Ma, Wang, Li, Zhang, Rao, & Han (2014) identified that the brain activity associated with cognitive and affective processes was linked to specific cultural value (e.g., interdependence) between individuals. Another paradigm using ‘cultural priming’ to examine the mediating effect between brain activation and cultural values revealed that priming interdependent versus independent self-construal led to changes of brain activity relating to self vs. face recognition (Sui and Han, 2007). Furthermore, exposure to pictures of cultural icons between the Eastern and the Western societies to bicultural individuals resulted in changes in brain activations associated with reflection of personality traits of oneself and one’s mother (Ng, Han, Mao, & Lai, 2010). These findings provide supporting evidence of a potential causal relationship between cultural values and a range of human cognitions. Importantly, Chen, Wagner, Kelley, Powers, & Heatherton (2013) found that immigrants showed dissimilar brain activity compared with subjects having the same ethnic background but developed in distinct cultural contexts (see Zuo and Han, 2013, for similar findings). As a result, evidence from cultural neuroscience suggests the importance of experience (in this case, culture, in a broader scale) that contributes to human cognitive functions.

Altogether, the thesis has used a range of approaches to highlight functional and structural variation within the PFC region and the mental abilities it supports. All three major sections of the thesis demonstrate some principles of organisation that exist across individuals, but also highlight the differences in a range of functions that could occur between TD individuals, between populations of individuals (TD vs. ASD), and between cultures of TD individuals (Taiwanese vs. British).

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